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# Endovascular Cooling for Moderate Hypothermia in Patients With Acute Stroke

## First Results of a Novel Approach

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***Background and Purpose***—We undertook this study to evaluate the feasibility of inducing and maintaining moderate hypothermia with the use of endovascular rather than surface cooling.

***Methods***—Six patients with severe acute ischemic stroke were treated with moderate hypothermia. This was induced and maintained by circulating temperature-adjusted normal saline in a closed-loop system entailing 3 balloons located near the tip of a central line, which dwelled in the inferior vena cava.

***Results***—The mean±SD initial temperature of the patients was 37±1°C (range, 35.5°C to 38.4°C). The pace of cooling was 1.4±0.6°C/h , and target temperature was reached after 3±1 hours (range, 2 to 4.5 hours). During hypothermia, the maximal temperature observed was 33.4°C, and the minimal temperature was 32.2°C. Temperature deviations >0.2°C or >0.3°C were observed during 21% or 10% of the hours under hypothermia, respectively. Singultus was the only device-related complication encountered. Pulmonary infection, arterial hypotension, bradycardia, arrhythmia, and thrombocytopenia were the most common side effects.

***Conclusions***—Induction and maintenance of hypothermia with an intravenous cooling device are feasible. The safety of this approach remains to be evaluated. **(*Stroke*. 2001;32:2550-2553.)**

**Key Words:** stroke, acute ■ stroke management

The neuroprotective properties of moderate hypothermia in acute ischemic stroke were demonstrated in several experimental models. The pathophysiological mechanisms involved include stabilization of the blood-brain barrier,[1–3] downregulation of cerebral metabolism,[4] and decrease of excitatory amino acids.[5,6] Additionally, preliminary clinical findings suggested that moderate hypothermia may influence mortality in patients with malignant middle cerebral artery infarction.[7,8] Currently, hypothermia is being induced by surface cooling with the use of cooling blankets, alcohol applied to exposed skin, or ice bags to groin, axilla, and neck. This approach, however, requires intensive effort from the medical and nursing staff for induction as well as maintenance of the target temperature.

Recently, an alternative approach based on intravenous cooling was proposed. A custom-built central line is advanced in the inferior vena cava. Normal saline is circulated through 3 balloons located near the tip of this line in a closed-loop system. Temperature regulation is achieved by adjusting the temperature of the circulating saline by a temperature-managing device.

We undertook this study to evaluate the potential of intravenous cooling for induction as well as maintenance of moderate hypothermia (33°C).

## Subjects and Methods

A total of 6 patients (5 men and 1 woman aged 64.5±8.4 years) with an ischemic infarction involving at least two thirds of the territory of the left (n=5) or right (n=1) middle cerebral artery were treated with moderate hypothermia according to our institutional protocol. All patients were sedated with midazolam at the time of the study; fentanyl was used for analgesia and atracurium for neuromuscular blockade. Alpha-stat was used for acid-base management. Patients lay in the 30° head-up position and were ventilated with a volume-controlled, pressure-regulated mode and an inspiratory/expiratory ratio of 1:2 (Servo Ventilator 300, Siemens). Room temperature in the intensive care unit was between 18°C and 20°C.

An 8.5F 35-cm catheter central line with a single infusion lumen (ICY, Alsius Corporation) was used in this study. In addition to the infusion lumen, the catheter consists of 1 additional lumen, which ends in 3 balloons sized 8×5×5 mm in diameter, located at the distal end of the catheter. These balloons are perfused with a sterile solution of normal saline via a closed-loop tubing system. Saline flow within the balloons creates a proprietary vortex flow pattern, aimed at maximizing heat exchange. The tubing is connected to a mobile temperature-management device (CoolGard, Alsius Corporation), which was placed at the patient's bedside. This device consists of a water bath, whose temperature can be adjusted between 0.5°C and 42°C, depending on the patient's temperature. A pump circulates the saline solution through the water bath. The catheter is inserted in the femoral vein and advanced to the inferior vena cava (abdominal x-ray of patient 5 displaying catheter position is shown in Figure 1).

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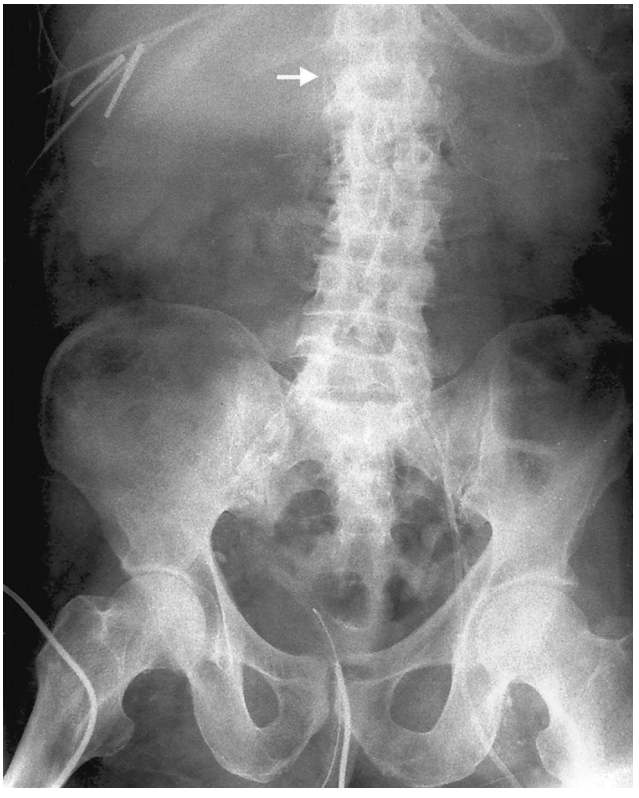

**Figure 1.** X-ray of patient 5 at 12 hours after catheter insertion. The tip of the catheter dwells in the inferior vena cava (arrow).

The protocol of this study was approved by the local ethics committee; all data were analyzed without patient identification. Hypothermia was induced as soon as possible; no limitations were set on the rate of cooling. No upper time limit was set for induction of moderate hypothermia after acute ischemic stroke; this decision was met at the discretion of the treating physicians. Duration of moderate hypothermia in our institution varies between 48 and 72 hours. The standard rewarming rate was at 1°C/8 h, while the maximal rate was 0.2°C/h. The exact time course of rewarming, as well as the duration of hypothermia, varied greatly depending on the intracranial pressure. Therefore, no standardized approach regarding the rewarming procedure could be established. Because of the individual variations among the 6 patients, the performance of the endovascular cooling device was not evaluated for the rewarming period. Furthermore, the slow rewarming pace used prevented us from examining the rate of rewarming feasible with this device.

Mean arterial pressure was invasively monitored by means of a catheter inserted in the radial artery. Intracranial pressure was monitored by parenchymal (Spiegelberg III; Spiegelberg pneumatic transducer, Spiegelberg AG) catheters, inserted ipsilateral to the affected hemisphere. A Foley temperature catheter for bladder temperature reading with a temperature resolution of 0.1°C was used for monitoring of body core temperature (Mon-a-therm, Mallinckrodt) in all cases. The patient's temperature was registered online with the use of dedicated software, with a sample rate of 1 value every 60 seconds. Subsequently, mean temperature values for each hour were calculated; only these values were used for further analysis.

The lower limit of cerebral perfusion pressure tolerated was 70 mm Hg; crystalloid or colloid fluids were used as first choice to increase arterial blood pressure, followed by vasopressors when necessary. Fluid homeostasis was maintained by exact evaluation of fluid intake and output, aiming at a central venous pressure between 8 and 12 cm $H_2O$. Parenteral nutrition or enteral feeding was begun as soon as possible.

Side effects previously reported in relation to hypothermia, such as pneumonia (diagnosed on the basis of new infiltrates on chest x-ray, purulent tracheobronchial secretions, or impairment of pulmonary gas exchange), coagulation disorders, bradycardia (<40 beats per minute), cardiac arrhythmia, and arterial hypotension (mean arterial blood pressure <80 mm Hg) were documented. Platelet count, serum levels of liver and pancreas enzymes, and electrolytes were determined every 12 hours. Although side effects are mentioned in this report, they are not evaluated further because the purpose of the present study was to examine the efficacy rather than the safety of this alternative approach.

The following parameters were evaluated: (1) time required to reach the target temperature of 33°C and, since the initial temperatures of the patients varied, the pace of cooling, expressed as degrees Celsius temperature drop per hour, and (2) the ability to maintain the target temperature over time based on the observed variations in temperature (maximal and minimal values recorded during the hypothermic period, as well as percentage of observations demonstrating temperature variations >0.2°C or >0.3°C).

## Results

Two patients had undergone systemic thrombolysis with 71 and 63 mg recombinant tissue plasminogen activator at 29 and 32 hours before catheter insertion, respectively. No recanalization of the occluded middle cerebral artery was observed in these cases. In 1 patient, severe bradycardia (<20 beats per minute) was observed during the first 4 hours at 33°C. Therefore, target temperature was subsequently set at 34.5°C. The data of this patient were included in the analysis concerning the rate of hypothermia induction and also the stability of temperature, but not in the graphic display of the time course of temperature. Clinical characteristics and side effects in the 6 patients treated with moderate hypothermia are shown in the Table.

The time required for catheter insertion ranged from 10 to 20 minutes. The initial temperature of the 6 patients was 37±1°C (mean±SD; range, 35.5°C to 38.4°C). Latency between onset of symptoms and initiation of hypothermia was 28.2±17 hours (mean±SD; minimum, 12 hours; maximum, 58 hours). The pace of cooling was 1.4±0.6°C/h (mean±SD; minimum, 0.8°C/h; maximum, 2.2°C/h); target temperature was reached after 3±1 hours (mean±SD; range, 2 to 4.5 hours). During hypothermia, the maximal temperature observed was 33.4°C, and the minimal temperature was 32.2°C. The mean duration of hypothermia was 67±13 hours (range, 50 to 78 hours). The total duration of hypothermia in all patients was 404 hours. Temperature deviations >0.2°C or >0.3°C were observed during 84 (21%) or 40 hours (10%), respectively. The time course of temperature values during induction and maintenance of hypothermia is displayed in Figure 2. No additional external cooling devices were used in any of the 6 patients during intravenous cooling. Furthermore, no antipyretics were applied in any case during the study period.

Five patients survived the acute phase of stroke; 1 patient died 59 hours after initiation of hypothermia because of uncontrollable intracranial hypertension.

Insertion site was the right femoral vein in 5 patients and the left in 1 patient. No groin hematomas were observed in association with catheter insertion in any case. Bradycardia occurred in 3 cases, with heart rates <20, 30, and 35 beats per minute, respectively. Additionally, ventricular extrasystole

**Clinical Characteristics and Side Effects in 6 Patients Treated With Moderate Hypothermia**

| Pt No./Age, y/Sex | Pt Height, cm/Weight, kg | Latency, h* | Initial Temperature, °C | Rate, °C/h† | Induction of Hypothermia, min‡ | Duration of Hypothermia, h§ | Side Effects |
|---|---|---|---|---|---|---|---|
| 1/53/M | 175/90 | 24 | 36.2 | 1.1 | 160 | 48 | Arrhythmia, pneumonia, hypokalemia, singultus |
| 2/74/M | 180/95 | 13 | 35.5 | 0.8 | 186 | 78 | Bradycardia (<30 bpm), pneumonia, thrombocytopenia, singultus |
| 3/72/M | 185/95 | 38 | 36.9 | 2 | 117 | 75 | Bradycardia (<40 bpm), pneumonia, hypokalemia, singultus |
| 4/56/M | 170/65 | 12 | 36.9 | 1.1 | 212 | 76 | Bradycardia (<40 bpm), pneumonia, singultus |
| 5/66/M | 185/95 | 24 | 38.4 | 2.2 | 143 | 72 | Arrhythmia, pneumonia, thrombocytopenia, singultus |
| 6/66/F‖ | 165/75 | 58 | 37.1 | 0.9 | 273 | 55 | Arrhythmia, pneumonia, singultus |

*Time between onset of symptoms and initiation of hypothermia.
†Temperature decrease in degrees Celsius per hour during induction of hypothermia.
‡Duration from initiation of cooling until 33°C was reached.
§Total duration of hypothermia.
‖This patient died on day 5 after stroke onset.

was observed in 3 patients. All patients required catecholamines for maintenance of arterial blood pressure; a combination of noradrenaline and dobutamine was applied. Pulmonary infection was diagnosed in all patients. Platelet count decreased in all patients during hypothermia; thrombocytopenia occurred in 2 cases (63 000 and 94 000 platelets per cubic millimeter) but did not require specific treatment in any case. No coagulopathy was observed in our study; the international normalized ratio of the patients treated with moderate hypothermia varied between 1.1 and 1.3. Serum levels of amylase were slightly elevated in 4 (<250 U/L) and moderately elevated (435 and 525 U/L) in the remaining 2 patients. Hypokalemia was observed in 2 patients (minimal values of 3.0 and 3.3 mval/L); potassium was substituted intravenously in both cases. Finally, singultus, probably due to irritation of the diaphragma through the cool solution, was observed in all patients.

## Discussion

Hypothermia is emerging as a promising treatment for intracranial hypertension in patients with acute ischemic stroke. Currently, induction of hypothermia and maintenance of target temperature are achieved through external cooling. Schwab et al[7] initially described this approach in 25 patients with acute ischemic stroke; time required for cooling to 33°C was 3.5 to 6.2 hours. No data were provided on the stability of temperature during the hypothermic period. Similar results were reported by Metz et al[9] (required time for target temperature of 32.5°C to 33°C of 2.3 to 4.5 hours in 10 patients with closed head injury), Baker et al[10] (cooling of 15 patients undergoing craniectomy to 34.3±0.4°C at a rate of 1±0.4°C/h), and Zeiner et al[11] (required time for cooling to 33°C of 4 hours in 27 patients admitted after cardiac arrest). The recent report of Clifton et al[12] describes results from the first large-scale study on moderate hypothermia, in which 199 head-injured patients were treated. Approximately 4 hours were required for cooling, while the mean body temperature during the first 48 hours of hypothermia was 33.2±1°C. Interestingly, Mayer et al[13] reported significantly poorer results, with a failure rate of 42%, using a combination of cooling blankets and acetaminophen for fever control. The preliminary results of the endovascular approach evaluated in our study are thus comparable to or slightly better than those obtained by external cooling, since the time required for

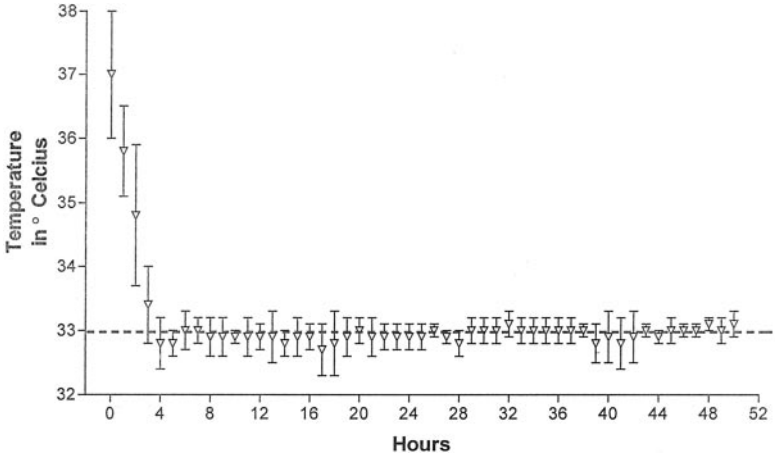


**Figure 2.** Temperature course during induction and maintenance of hypothermia in 6 patients with acute stroke. Induction of hypothermia begins at 0 hours. Data from patient 2 are only included during the first 5 hours. Plotted data between 6 and 50 hours of hypothermia are derived from the remaining 5 patients.

hypothermia induction was 3±1 hours; approximately 15 additional minutes must be calculated for catheter insertion. An alternative method using venovenous extracorporeal circulation was introduced by Piepgras et al.[14] While the target temperature of 32°C was reached after 113±81 minutes, the invasiveness of this approach limits its applicability.

Maintenance of temperature was also feasible, with maximal variations of −0.8°C to 0.4°C and temperature deviations <0.3°C during 90% of the hypothermic period. A major advantage of the endovascular approach is the fact that it requires minimal effort from the nursing staff because no further measures are necessary after catheter insertion. It must be noted that the duration of moderate hypothermia in this study varied among the enrolled patients. According to our institutional protocol, moderate hypothermia should be applied for 48 to 72 hours. This relatively long treatment period derives from the observation that brain edema formation reaches its maximum between the third and fourth day after cerebral infarction.[15] Furthermore, some experimental studies suggest a benefit of prolonged cooling after focal cerebral ischemia.[16,17] Still, individual decisions are often necessary, particularly in dependence on the course of intracranial pressure. Because the sole purpose of this preliminary study was to evaluate the feasibility of endovascular cooling, we refrained from applying stricter enrollment criteria.

Although the low number of examined patients allows no statements concerning safety issues, the fact that the only specific device-related side effect was singultus is encouraging. All the other side effects encountered in our study have been previously described in association with moderate hypothermia in patients with acute stroke.[7,8] No groin hematomas were observed, which is particularly important when one considers that 2 patients had been treated with intravenous thrombolytics 29 and 32 hours before catheter insertion.

In conclusion, intravascular cooling presents an attractive alternative for induction of moderate hypothermia, which appears to be at least as fast and less time consuming than surface cooling.

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