Induction and Maintenance of Mild Hypothermia by Surface Cooling in Non-intubated Subjects

Richard M. Zweifler, MD,* Marc E. Voorhees, PhD,† M. Asim Mahmood, MD,* and Debra D. Alday, RN, BSN *

Mild induced hypothermia holds promise as an effective therapy for acute ischemic stroke. We developed a novel strategy to rapidly induce and maintain mild hypothermia in unanesthetized, non-intubated subjects as a model for the treatment of acute stroke patients. We induced and maintained mild hypothermia (tympanic membrane temperature 34°C-35°C) for over 5 hours in 10 healthy volunteers. All subjects received 1000 mg of acetaminophen orally and meperidine intravenously for comfort and suppression of shivering. In phase 1, subjects (n=5) were cooled using Arctic Sun Energy Transfer Pads (Medivance, Inc., Louisville, CO) with manual temperature control. In phase 2, subjects (n=5) were cooled using the Arctic Sun® Energy Transfer Pads™ connected to the Arctic Sun Model 200 Temperature control module (Medivance, Inc.). Core temperatures were measured at the tympanic membrane and rectum. All subjects reached the target tympanic temperature range. The mean time to reach a tympanic temperature of 35°C was 90±53 minutes (1.4°C/hour) in phase 2. The most common side effect was nausea, observed in 30% of subjects. There was no statistically significant change in heart rate, blood oxygenation, or diastolic blood pressure compared with baseline; systolic blood pressure was significantly elevated for the 180 minute time point only (140±20mm Hg vs 122±13mm Hg; P = .042). We developed a method to rapidly and comfortably induce and maintain mild hypothermia in unanesthetized, non-intubated humans. Further study to optimize the pharmacologic inhibition of thermoregulation and to assess tolerability over longer durations is warranted.

Key Words: Body temperature—cerebrovascular disorders—hypothermia—stroke management—surface cooling.

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Stroke is the second leading cause of mortality worldwide.¹ In the United States alone, there are an estimated 731,000 new cases annually.² Intravenous tissue plasminogen activator (t-PA) is currently the only Food and Drug Administration-approved therapy for acute ischemic stroke, but only a minority of stroke patients (an estimated 1-2% nationally) qualify for and receive it.³-⁵ In addition, the absolute clinical benefit of t-PA for stroke is only modest, and its administration carries significant potential complications (i.e., hemorrhagic transformation). Additional therapies for acute stroke are, therefore, desperately needed.

Experimentally, mild-moderate hypothermia is neuroprotective following both global and focal cerebral ischemia,⁶-¹³ and clinical studies have established body temperature as an independent predictor of post-stroke morbidity and mortality.¹⁴-¹⁸ These findings have led to preliminary experience with therapeutic induced hypothermia for stroke. The majority of clinical experience is limited to patients with malignant stroke requiring intubation, paralysis, and sedation to overcome thermoregulatory responses.¹⁹-²² Such invasive techniques are less...
than optimal, as only a minority of stroke patients would otherwise require intubation.²³ An ideal therapy is widely applicable (to include patients with both moderate and severe deficits) and minimally invasive. Endovascular techniques are under investigation, but these devices are invasive. Surface cooling with forced-air devices has been studied,²⁴²⁶ but established methods do not permit rapid cooling to the depths likely necessary to be therapeutic (2-3°C). We sought to develop a novel strategy to rapidly induce and maintain mild hypothermia in unanesthetized, non-intubated subjects as a model for the treatment of acute stroke patients.

Materials and Methods

The study was divided into two phases. In the feasibility phase (phase 1), the goals were to determine if healthy volunteers could be simply, rapidly, and comfortably cooled to 34°C-35°C using Arctic Sun Energy Transfer Pads™ (Medivance, Inc., Louisville, CO) and to develop a pharmacologic protocol for shivering suppression and comfort. In the evaluation phase (phase 2), the goals were to demonstrate the induction and maintenance of mild hypothermia (34-35°C) in healthy volunteers using the Arctic Sun Temperature Management System (Model 200; Medivance, Inc., Louisville, CO) and to validate the pharmacologic protocol for shivering suppression.

The Arctic Sun Energy Transfer Pads consist of tri-layer construction. The outermost layer is flexible closed cell foam with molded fluid channels. The outermost layer also acts to insulate the circulating water from ambient conditions. The middle layer is a polymeric film that is laminated to the outer layer to seal the thin fluid channels. The inner layer is a biocompatible hydrogel that adheres to the patient’s skin on application and provides intimate pad to skin contact for efficient heat transfer. Temperature-controlled water flows through the pads under negative pressure at a flow rate of approximately 1 liter per minute per pad, resulting in heat exchange from the water to or from the subject. In both phases, approximately 0.5 m² to 0.6 m² of body surface area was covered.

The Arctic Sun Temperature Management System is comprised of Arctic Sun Energy Transfer Pads and a control module. The control module interfaces with a commercially available chiller (Kodiak Recirculating Chiller Model RC006G03AA2C010; Lytron, Woburn, MA) and regulates the water temperature flowing through the energy transfer pads. Patient temperature set points are programmed in the control module. Controller water temperature is automatically adjusted via a feedback algorithm to achieve the desired patient target temperature. In phase 2, the rectal temperature was the controlled temperature.

After obtaining approval from the Institutional Review Board at the University of South Alabama, healthy volunteers were recruited. Exclusion criteria included any of the following: history of cryoglobulinemia, paramyotonia congenita, recent myocardial ischemia, pregnancy, or recent use of phenothiazines, MAO inhibitors, alcohol, or narcotics. Females of childbearing potential were screened with a urine pregnancy test. All subjects underwent cardiac and neurologic examinations and 12-lead electrocardiography before the initiation of cooling.

Feasibility Phase (Phase 1)

Four Arctic Sun Energy Transfer Pads were applied to the thighs and chest and connected to a heater-cooler (Hemotherm Dual Reservoir Cooler/Heater Model #400M; Cincinnati Sub Zero Products, Inc., Cincinnati, OH). Core temperatures were measured at the tympanic membrane and rectum. Mean skin-surface temperature was determined from the weighted average of calf, thigh, chest, and upper arm skin temperatures.²⁷ Thermoregulatory vasoconstriction was evaluated using forearm minus fingertip skin-temperature gradients.²⁸ Temperatures were measured using Mon-a-Therm thermocouple probes connected to Mallinckrodt Model 6510 two-channel electronic thermometers having an accuracy near 0.1°C (Mallinckrodt Anesthesia Products, St. Louis, MO). Temperatures were recorded before cooling was started (i.e., baseline) and subsequently at 15-minute intervals.

A single oral dose of 1000 mg of acetaminophen was administered within 20 minutes before treatment and a bolus of intravenous (IV) meperidine (25-75 mg) was given within 5 minutes of the start of cooling. Two subjects also received initial IV doses of 12.5 mg to 25 mg chlorpromazine. Active cooling was initiated and the inlet water temperature was manually controlled to achieve a target tympanic temperature between 34°C and 35°C. Additional doses of meperidine and/or chlorpromazine were administered to maintain comfort and to prevent shivering. Active cooling and maintenance of hypothermia continued for up to 5 hours; subjects were actively re-warmed to a tympanic temperature of 36°C.

The presence of shivering was noted on physical examination, electromyographic artifact on continuous electrocardiography (ECG), or by subject report. Overall thermal comfort was evaluated at 15-minute intervals with a 100-mm-long visual analog scale (VAS) on which 0 mm defined the worst imaginable cold, 50 mm identified thermal neutrality, and 100 mm indicated unbearable heat. A new, unmarked scale was used for each assessment. Heart rate and oxyhemoglobin saturation were monitored using ECG and pulse oximetry; arterial blood pressure was recorded oscillometrically at 15-minute intervals.

Evaluation Phase (Phase 2)

Five Arctic Sun Energy Transfer Pads were applied to the thighs, back, and abdomen and connected to an Arctic
Sun Model 200 Temperature control module with inter-facing recirculating chiller (Kodiak). Temperatures were measured in the same manner as in phase 1, except that the rectal temperature probe was attached to the Arctic Sun Control Module. The rectal temperature signal was used by the control module to adjust inlet water temperature via a feedback control algorithm to achieve a target temperature of 34.5°C.

A single oral dose of 1000 mg acetaminophen was administered within 20 minutes before treatment. A bolus of IV meperidine (50-100 mg) was given within 5 minutes of the start of cooling. Additional doses of meperidine were administered to maintain comfort and to prevent shivering. Active cooling and maintenance of hypothermia continued for 5 hours. As in phase 1, the subjects were actively re-warmed to a tympanic temperature of 36°C before termination of the experiment. Shivering, comfort, oxyhemoglobin saturation, and arterial blood pressure were recorded as in phase 1.

Results are expressed as mean ± SD. Student t test was performed to compare mean dosages of meperidine in the 2 phases. One way repeated measures analysis of variance (ANOVA) was performed to compare heart rate, diastolic blood pressure, arterial oxygen saturation, and comfort to baseline (pre-cooling). A value of \( P < .05 \) was considered statistically significant.

### Results

Five subjects were enrolled in phase 1. Subject characteristics are summarized in Table 1. Mild hypothermia was attained in all subjects. The mean time to reach a tympanic temperature of 35°C was 77 ± 23 minutes, which corresponded to a mean cooling rate of 1.5 ± 0.6°C/hour. Details of the cooling responses of the individual subjects are presented in Table 2. The mean total dosage of meperidine was 280 ± 155 mg. Only subjects #1 (37.5mg) and #2 (12.5mg) received chlorpromazine.

Six subjects were enrolled in phase 2. One subject was withdrawn from the study before the initiation of cooling because of a vasovagal syncope at the time of IV insertion. Subject characteristics are presented in Table 1. The mean time to reach a tympanic temperature of 35°C was 90 ± 53 minutes, corresponding to a mean cooling rate of 1.4 ± 0.4°C. Details of the cooling responses of the individual subjects are presented in Table 2. The mean total dosage of meperidine was 370 ± 91 mg. The tympanic and rectal temperatures over time are shown in Figure 1.

In all subjects, there was no statistically significant change in heart rate, diastolic blood pressure, or blood oxygenation compared with baseline. Systolic blood pressure was significantly elevated compared with baseline only for the 180 minute timepoint (140 ± 20 v 122 ± 13 mm Hg; \( P = .042 \)). The mean total meperidine dosage in phase 2 was 90 mg higher than in Phase 1 (370mg v 280mg; \( P = .28 \)). Comfort was statistically significantly lower than baseline for all timepoints during active cooling (except T = 135 min; Fig 2). Although subjects felt colder than normal, they universally reported that it was tolerable; none requested that the study be terminated.

### Discussion

Interest in therapeutic induced hypothermia is growing, although the accumulating clinical experience is largely limited to moderate hypothermia in intubated and anesthetized patients. Schwab et al\(^1\) induced hypothermia as a treatment to reduce intracranial pressure (ICP) in 25 patients with severe middle cerebral artery infarction. Using forced air (Polar Bair; Augustine Medical, Eden Prairie, MN), patients were cooled to a bladder temperature of 33°C to 34°C for 48 to 72 hours. Although
hypothermia was effective at lowering ICP, patients experienced a rebound increase in ICP after rewarming. More recently, Schwab et al.\(^{19}\) reported a multicenter experience with induced hypothermia for the management of increased ICP in massive hemispheric infarction. Fifty patients were cooled via the surface to 32\(^\circ\)C to 33\(^\circ\)C for 24 to 72 hours. A rebound rise in ICP with rewarming was observed, as were several other side effects such as cardiac failure, coagulopathy, hypotension, arrhythmias, and pneumonia. Naritomi et al.\(^{29}\) cooled 4 thrombolyzed stroke patients via cooling blankets and alcohol compresses to a jugular bulb temperature of 33\(^\circ\)C for between 3 and 5 days without serious adverse effects. Krieger et al.\(^{22}\) reported their experience with surface cooling 10 stroke patients, all of whom had received thrombolysis, to a bladder temperature of 32\(^\circ\)C for 12 to 72 hours (mean of 47 hours). Overshoot of the target temperature was noted in the majority of patients, although no serious side effects were encountered. Most recently, Georgiadis et al.\(^{20}\) reported the clinical course of 19 patients with severe ischemic stroke who were cooled to a target temperature of 33\(^\circ\)C by either a surface (n=11) or endovascular technique (n=8). Rebound elevation in ICP was observed as were a high incidence of serious side effects (e.g., pneumonia, arrhythmia, thromboocytopenia, and hypokalemia). It is possible that less aggressive cooling (i.e., mild hypothermia) will reduce the incidence of adverse events.

We have developed a method to rapidly induce and maintain mild hypothermia in unanesthetized, non-intubated humans. To our knowledge, the Arctic Sun represents the first reported non-invasive strategy to achieve core temperatures below 35\(^\circ\)C in the absence of anesthesia. Previous attempts at surface cooling of awake stroke patients have produced slow cooling rates and modest cooling depths. Zweifler and Sessler\(^{26}\) reported only a 1.2\(^\circ\)C drop (0.6\(^\circ\)C/hr) in tympanic temperature using the PolarAir (Augustine Medical) forced air device in combination with meperidine and chlorpromazine. Kammersgaard et al.\(^{24}\) achieved 1.3\(^\circ\)C decline in tympanic

<table>
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<th>Phase</th>
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Abbreviations: \(T\), tympanic membrane temperature.

Table 2. Cooling responses of subjects

![Figure 1. Mean tympanic (closed triangles) and rectal temperatures (closed diamonds) for subjects in phase 2. Error bars represent one standard error of the mean.](image-url)
membrane temperature with a cooling rate of 0.22°C/hour, using the Polar Air and meperidine. Meijer et al. reported a 1.25°C (0.16°C/hr) drop in rectal temperature using a cooling blanket and midazolam drip with or without an alcohol sponging. In the present study, we rapidly achieved and maintained tympanic membrane temperatures between 34°C and 35°C. The 35°C threshold was achieved in a mean of 90 ± 53 minutes with a mean cooling rate of 1.4 ± 0.4°C/hour. This cooling rate compares favorably with the 1.4°C/hr rate reported by Georgiadis et al. using an endovascular approach. Surface cooling may be a more attractive clinical option than endovascular cooling as it is non-invasive, does not require specially-trained personnel to implement, and may thus be initiated more rapidly. We have also shown that stable core temperatures can be achieved during maintenance of hypothermia using a surface technique.

Surface cooling of unanesthetized humans requires overcoming effective thermoregulatory defenses, most notably shivering. A difficulty with surface cooling is that vasoconstriction and shivering thresholds are negatively linearly related to skin temperature, with mean skin temperature representing approximately 20% of the total regulatory input. As a result, thermal input from cutaneous temperature receptors triggers regulatory responses at relatively high core temperatures during surface cooling. Furthermore, normal thermoregulatory responses have been demonstrated in patients with mild to moderate ischemic strokes. Zweifler and Sessler studied induction of mild hypothermia in 8 patients with ischemic stroke via surface cooling with forced-air. The mean vasoconstriction and shivering thresholds were 37.2°C and 36.6°C, respectively. No patient reached the target core temperature of 34°C; the lowest measured shivering threshold was 36.2°C. As meperidine has a special antishivering effect, we used IV meperidine to suppress shivering and to maintain comfort. Although no respiratory compromise was observed (the most worrisome potential side-effect of meperidine) we did observe nausea in 30% of subjects. All cases of nausea occurred in phase 2, making the trend toward a higher total meperidine dosage in phase 2 noteworthy. A different pharmacologic strategy to overcome thermoregulatory defenses may be more desirable. For example, combination therapy with another agent (e.g., buspirone, α-2 agonist, or 5-hydroxytryptamine agonist) may permit a lower total dosage of meperidine for shivering suppression, which may also reduce the likelihood of nausea. Buspirone has been shown to have a synergistic effect on lowering the shivering threshold when administered in combination with meperidine. Ondansetron, a 5-hydroxytryptamine3 agonist, is of particular interest as it has been shown to suppress post-operative shivering and it is a powerful anti-emetic. Further study evaluating the combination of meperidine with these or other thermoregulatory inhibitory agents is warranted.

The potential therapeutic window and the optimal depth and duration of therapeutic hypothermia remain unknown. We chose a target tympanic membrane temperature of 34.5°C as preclinical studies indicate that as little as 1°C to 3°C hypothermia is neuroprotective. In addition, mild hypothermia to this level should reduce the likelihood of treatment-related side-effects such as arrhythmias, coagulopathies, and infections and may reduce the incidence of rebound elevated ICP; slow, controlled rewarming, which is also feasible with the Arctic Sun, may also be of benefit. It is noteworthy that our subjects experienced no significant changes in heart rate and blood oxygenation and no arrhythmias were observed. Furthermore, blood pressure (systolic) was significantly elevated at a single timepoint only. As regards duration of therapy, additional study is required to investigate the tolerability of the Arctic Sun over a longer time period (e.g., 12 to 24 hours).

Our study included fairly young, healthy volunteers. The efficacy and tolerability of this technique in stroke patients remains unproven but is currently being evaluated. The role of therapeutic hypothermia may extend beyond acute stroke, however. Recently, induced hypothermia was shown to improve clinical outcomes in pa-
tients with cardiac arrest, and there are conflicting data regarding the efficacy of hypothermia for head trauma. Therapeutic hypothermia for myocardial infarction is also under investigation. Simple, safe, and reliable methods to induce and maintain therapeutic hypothermia are needed.

In conclusion, we developed a novel method to rapidly and comfortably induce and maintain mild hypothermia in unanesthetized, non-intubated humans. Further study to optimize the pharmacologic inhibition of thermoregulation, and to assess tolerability over longer durations, is warranted.

References


