Thermoregulatory Vasoconstriction and Shivering Impede Therapeutic Hypothermia in Acute Ischemic Stroke Patients

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Objectives. We tested the hypothesis that vasoconstriction and shivering thresholds are sufficiently reduced by acute stroke to permit induction of therapeutic hypothermia without additional pharmacological inhibition of thermoregulatory control.

Methods. We studied eight patients 2 ± 1 days after ischemic stroke. Forced-air cutaneous cooling was administered until the patients shivered continuously or reached a tympanic membrane (ie, core) temperature of 34°C. The tympanic membrane temperatures triggering vasoconstriction and shivering identified the thresholds for each response. Results. Patients had a mean age of 68 ± 8 years and a mean National Institutes of Health Stroke Scale (NIHSS) score of 5. No patient reached the target core temperature of 34°C. Vasoconstriction and shivering thresholds were 37.1 ± 0.4°C and 36.6 ± 0.4°C, respectively. Conclusions. Vasoconstriction and shivering were initiated at roughly normal temperatures in ischemic stroke patients, and these thermoregulatory responses prevented induction of therapeutic hypothermia. Pharmacological reduction of the vasoconstriction and shivering thresholds will be required if therapeutic hypothermia for stroke patients is to be induced easily by surface cooling. Key Words: Cerebral infarction—Thermoregulation—Vasoconstriction—Shivering—Temperature—Hypothermia—Brain protection.

Mild hypothermia apparently provides multifactorial protection against cerebral ischemia. Hypothermia decreases cerebral metabolic rate, but this decrease is unlikely to be the primary protective action because drugs that similarly decrease metabolic rate provide consider-

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potential limitation of therapeutic hypothermia, however, is the triggering of thermoregulatory vasoconstriction, which decreases cutaneous heat loss\textsuperscript{17} and constrains metabolic heat to the core thermal compartment.\textsuperscript{18} Hypothermia also triggers shivering, which increases heat production two-fold to five-fold.\textsuperscript{19,20} These effective responses usually prevent core hypothermia, even during moderate to severe cold exposure.\textsuperscript{21} Therefore, induction of therapeutic hypothermia is difficult unless thermoregulatory vasoconstriction and shivering are prevented, as by general anesthesia\textsuperscript{22-24} or sedatives.\textsuperscript{25,26} An ideal stroke therapy, however, would not prevent adequate neurologic examination by reducing patients’ level of consciousness.

An alternative to pharmacological inhibition of thermoregulatory control is based on the knowledge that acute brain injury itself may prevent vasoconstriction and shivering. Furthermore, thermoregulatory control is impaired at advanced age, when stroke is suffered most commonly.\textsuperscript{27,28} Accordingly, we tested the hypothesis that the core temperatures triggering vasoconstriction and shivering are sufficiently reduced by acute stroke to facilitate induction of therapeutic hypothermia. Because thermal discomfort might also limit core cooling, we simultaneously evaluated patients’ perceptions of cold.

Materials and Methods

With approval from the Human Subjects Committee at the University of California, San Diego, and informed consent, we studied eight patients (seven men, one woman) 2 ± 1 (±SD) days after an ischemic stroke. No patient was pregnant, had evidence of recent myocardial ischemia, or had a history of paramyotonia congenita or cryoglobulinemia. Patients remained supine in a hospital bed for the duration of the study.

Patients were evaluated using the National Institutes of Health Stroke Scale (NIHSS) and given a single oral dose of acetaminophen, 1,000 mg, within 20 minutes before treatment. A full-length forced-air cover (model 300; Augustine Medical, Eden Prairie, MN) attached to a prototype forced-air cooler (Augustine Medical) was placed over the patient. This device injects air at ~14°C into the disposable cover at a rate of 1,000 L/min.\textsuperscript{29} Active cooling continued until core temperature reached 34°C or sustained shivering was observed.

Core temperatures were measured at the tympanic membrane because this site correlates well with brain,\textsuperscript{24} epidural,\textsuperscript{25} and intraventricular\textsuperscript{26} temperatures. After ophthalmoscopic confirmation that the ear canal was free of wax, the probe was inserted slowly until the patient felt the thermocouple touching the tympanic membrane; appropriate placement was confirmed when patients easily detected gentle rubbing of the attached wire. The probe was then securely taped in place, the ear canal occluded with cotton, and the external ear covered with a gauze bandage.

Mean skin-surface temperature was determined from the weighted average of calf, thigh, chest, and upper arm skin temperatures.\textsuperscript{30} One arm (the stroke-unaffected extremity, when appropriate) was kept exposed to the ambient environment and protected from direct cooling. Thermoregulatory vasoconstriction was evaluated on this arm using forearm minus fingertip, skin-temperature gradients. Gradients correlate well with fingertip blood flow;\textsuperscript{37} negative values of this index indicate vasodilation, whereas gradients exceeding 4°C identify intense vasoconstriction. Temperatures were measured using Mon-a-Therm thermocouple probes connected to Mallinckrodt model 6510 two-channel electronic thermometers with an accuracy near 0.1°C (Mallinckrodt Anesthesia Products, St Louis, MO). Baseline temperatures were recorded before cooling was started and subsequently at 10-minute intervals.

As in previous investigations,\textsuperscript{31} shivering was graded on a three-point scale, where 0 indicated no shivering, mild shivering was considered grade 1, and intense sustained shivering was grade 2. Overall thermal comfort was evaluated at 10-minute intervals using 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 electrocardiography and pulse oximetry; arterial blood pressure was recorded oscillometrically at 10-minute intervals.

The tympanic membrane temperature triggering a 4°C forearm minus fingertip skin-temperature gradient identified the vasoconstriction threshold. Similarly, the core temperature triggering sustained grade 1 shivering defined the shivering threshold. Results are expressed as mean ± SD; \( P < .05 \) was considered statistically significant for correlations.

Results

One patient did not shiver, even after 120 minutes of cooling at a minimum core temperature of 37.2°C. Because of intense thermal discomfort, another requested that the study be discontinued after only 20 minutes of cooling. Altogether, core temperature decreased only 0.5 ± 0.3°C during 103 ± 60 minutes of cooling, despite a decrease in mean skin temperature from 32.7 ± 0.8°C to 26.1 ± 1.9°C. No patient reached the target core temperature of 34°C.

The threshold for vasoconstriction was 37.1 ± 0.4°C at a mean skin temperature of 28.3 ± 2.8°C, and was observed after 27 ± 26 minutes of cooling. The threshold for shivering was 36.6 ± 0.4°C at a mean skin temperature of 26.1 ± 1.9°C and was observed after 103 ± 60 minutes of
implementation and safety. However, the technique is mala.

sufficiently to permit simple induction of core hypothermia. Moreover, skin is cooled far more than core cerebral ischemia itself impairs thermoregulatory control. Nonetheless, these core temperatures were well within the normothermic range and unlikely to provide any protection against ischemia. As expected from previous studies, thermoregulatory vasoconstriction and shivering prevented further hypothermia. Consequently, we failed to confirm our hypothesis that acute stroke may have caused some thermoregulatory inhibition. Nonetheless, these core temperatures trigger effective thermoregulatory defenses. However, all available methods of direct core cooling are invasive and unlikely to be generally applicable to stroke victims.

Limitations of this study are that our patients experienced mild to moderate strokes (the average patient missed 5 points on the NIHSS) and were evaluated >2 days after stroke onset. Although not supported by our data, thermoregulatory response thresholds may be reduced more in patients with more severe strokes or during the hours immediately after ischemic events. Alternatively, altered thermoregulation may be more a function of stroke localization; the lowest thermoregulatory thresholds were in a patient with a right-sided thalamic lacunar stroke (patient 2). Nonetheless, our results suggest that induction of therapeutic hypothermia will require pharmacological intervention in most patients.

One of the best methods of inhibiting thermoregulatory defenses is administration of general anesthesia. All anesthetics tested so far markedly impair thermoregulatory responses.33 Typical surgical doses of volatile anesthetics such as isoflurane and halothane increase the sweating threshold ~1°C34,35 but decrease the vasoconstriction threshold ~3°C.22,24 The result is an approximately 20-fold increase in the range of core temperatures not triggering protective thermoregulatory responses.33 Because anesthetized patients do not defend temperature alterations within this broad range, it is relatively easy to induce hypothermia. However, it is impractical to facilitate therapeutic hypothermia by administering volatile anesthetics to most stroke victims.

Fortunately, sedative doses of one anesthetic, propofol, produce substantial thermoregulatory inhibition. Previous studies nonetheless suggest that reduction of the vasoconstriction threshold to 34°C at a skin temperature of 26°C will require a plasma propofol concentration of ~8 µg/mL.26 This concentration produces substantial depression of the core temperature vasoconstriction and shivering thresholds ~-1.8°C. Direct core cooling would allow a greater reduction in brain temperature before triggering thermoregulatory defenses. However, all available methods of direct core cooling are invasive and unlikely to be generally applicable to stroke victims.

**Discussion**

Normal body temperature is near 37°C because small deviations trigger effective thermoregulatory defenses. The first and most important defense against hypothermia is arteriovenous shunt constriction. Vasoconstriction minimizes further core hypothermia by reducing cutaneous loss of heat and constraining metabolic heat to the core thermal compartment. The core temperatures that triggered vasoconstriction and shivering in our stroke patients were 37.1 and 36.6°C, respectively. These thresholds are slightly lower than would be expected in normal subjects with skin temperatures near 27°C,32 suggesting that acute stroke may have caused some thermoregulatory inhibition. Nonetheless, these core temperatures were well within the normothermic range and unlikely to provide any protection against ischemia. As expected from previous studies, thermoregulatory vasoconstriction and shivering prevented further hypothermia. Consequently, we failed to confirm our hypothesis that acute cerebral ischemia itself impairs thermoregulatory control sufficiently to permit simple induction of core hypothermia.

Obvious advantages of surface cooling include easy implementation and safety. However, the technique is also problematic because skin is cooled far more than core tissues. A difficulty with cutaneous cooling is that vasoconstriction and shivering thresholds are negatively linearly related to skin temperature, with mean skin temperature representing ~20% of the total regulatory input.32 As a result, thermal input from cutaneous temperature receptors triggers regulatory responses at relatively high core temperatures during surface cooling. In our patients, for example, cutaneous cooling from ~33 to ~26°C would increase the core temperature vasoconstriction and shivering thresholds ~1.8°C. Direct core cooling would allow a greater reduction in brain temperature before triggering thermoregulatory defenses. However, all available methods of direct core cooling are invasive and unlikely to be generally applicable to stroke victims.

**Table 1. Patient characteristics and thermoregulatory thresholds**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>NIHSS score</th>
<th>Thres\textsubscript{vc} (°C)</th>
<th>Thres\textsubscript{sh} (°C)</th>
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</thead>
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<tr>
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<td>M</td>
<td>5</td>
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<tr>
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<tr>
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<td>M</td>
<td>2</td>
<td>37.3</td>
<td>37.2</td>
</tr>
</tbody>
</table>

Mean ± SD: 68 ± 8 — 5 ± 3 37.1 ± 0.4 36.6 ± 0.4

**NOTE.** Thres\textsubscript{vc}, vasoconstriction threshold; Thres\textsubscript{sh}, shivering threshold. Patient 3 tolerated only 20 minutes of cooling; patient 5 did not shiver after 120 minutes of cooling at a minimum core temperature of 37.2°C. There were no clinically important changes in oxyhemoglobin saturation, heart rate, or arterial blood pressure. Thermal comfort was measured in only five patients because two had visual field defects and another suffered weakness of the writing hand. Thermal comfort in the remaining patients averaged 50 ± 1 mm at baseline but decreased during the initial 10 minutes of cooling and then generally remained between 30 and 40 mm.
strokes do not reduce thermoregulatory response thresholds sufficiently to facilitate simple core cooling to potentially neuroprotective temperatures. General application of therapeutic hypothermia is thus likely to require pharmacological inhibition of thermoregulatory defenses.

References


