Neither Arm nor Face Warming Reduces the Shivering Threshold in Unanesthetized Humans

Anthony G. Doufas, MD, PhD; Anupama Wadhwa, MD; Chun-Ming Lin, MD; Yunus M. Shah, MD; Keith Hanni, BS; Daniel I. Sessler, MD

Background and Purpose—Hand warming and face warming, combined with inhalation of heated air, are reported to suppress shivering. However, hand or face temperature contributes only a few percent to control of shivering. Thus, it seems unlikely that manipulating hand or facial skin temperature alone would be sufficient to permit induction of therapeutic hypothermia. We tested the hypothesis that focal arm (forearm and hand) warming or lower facial warming, combined with inhalation of heated and humidified gas, only minimally reduces the shivering threshold (triggering core temperature).

Methods—We studied 8 healthy male volunteers (18 to 40 years of age) on 3 days: (1) control (no warming), (2) arm warming with forced air at \(43^\circ C\), and (3) face warming with 21 L/min of air at \(42^\circ C\) at a relative humidity of 100%. Fluid at \(4^\circ C\) was infused via a central venous catheter to decrease tympanic membrane temperature 1°C/h to 2°C/h; mean skin temperature was maintained at 31°C. A sustained increase in oxygen consumption quantified the shivering threshold.

Results—Shivering thresholds did not differ significantly between the control (36.7 \(\pm 0.1^\circ C\)), arm-warming (36.5 \(\pm 0.3^\circ C\)), or face-warming (36.5 \(\pm 0.3^\circ C\); analysis of variance, \(P=0.34\)) day. The study was powered to have a 95% probability of detecting a difference of 0.5 \(\pm 0.5^\circ C\) (mean \(\pm SD\)) between control and either of the 2 treatments at \(\alpha=0.05\).

Conclusions—Focal arm or face warming did not substantially reduce the shivering threshold in unanesthetized volunteers. It thus seems unlikely that these nonpharmacological modalities will substantially facilitate induction of therapeutic hypothermia. (Stroke. 2003;34:1736-1740.)

Key Words: body temperature regulation ■ shivering

Overwhelming evidence in animals indicates that even mild hypothermia provides substantial protection against cerebral and myocardial ischemia. Mild hypothermia has been shown to improve outcome after cardiac arrest in humans, and major randomized outcome trials are in progress to evaluate the potential benefits of mild hypothermia during aneurysm clipping and after stroke or acute myocardial infarction. Many of these studies target core temperatures between 33°C and 34°C.

Induction of hypothermia during surgery is relatively easy because anesthetics profoundly impair thermoregulatory responses. However, use of therapeutic hypothermia in stroke patients may be compromised because tiny reductions in core temperature trigger aggressive thermoregulatory defenses, even in stroke victims. Shivering is the most powerful autonomic cold defense in humans. This has led to a search for treatments that impair shivering without causing excessive toxicity. Many drugs inhibit shivering, but most are general anesthetics or major sedatives. For example, the combination of buspirone and meperidine significantly reduces the shivering threshold (triggering core temperature); however, meperidine doses sufficient to reduce core temperature to \(33^\circ C\) may be associated with respiratory toxicity.

An alternative to pharmacological treatment of shivering is surface warming. For example, Sweney et al recently reported that focal hand warming suppresses shivering in mildly hypothermic volunteers. The same group also reported that shivering can be suppressed by warming of the lower face, combined with inhalation of heated and humidified air. Others have also reported that facial warming reduces shivering, as does radiant heating of the face and upper chest.

The difficulty with these observations is that treatments reducing the shivering threshold only a couple tenths of a degree centigrade may be sufficient to attenuate shivering. Treatments that only slightly reduce the shivering threshold may appear to be effective in volunteers or postoperative patients but may be completely inadequate for
induction of therapeutic hypothermia. Skin temperature contributes \( \approx 20\% \) to autonomic control of shivering, with the remainder being derived from core temperature.\textsuperscript{24,25} However, the arms and face are a small portion of the total skin surface. It thus seems unlikely that manipulating hand or facial skin temperature alone would impair thermoregulatory responses sufficiently to permit induction of therapeutic hypothermia. Therefore, we tested the hypothesis that focal arm warming or lower facial warming, combined with inhalation of heated and humidified gas, only minimally reduces the shivering threshold.

Methods

With approval of the Human Studies Committee at the University of Louisville and informed consent, we studied 8 healthy male volunteers. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud’s syndrome.

Protocol

The volunteers fasted 8 hours before each study day. They were minimally clothed and rested supine on a standard operating room table. Ambient temperature was maintained at \( \approx 22^\circ \text{C} \). Each volunteer was studied on 3 days: (1) control (no warming), (2) lower-arm warming (forearm and hand), and (3) face warming. Each study day was separated by at least 48 hours.

The arm warming apparatus consisted of 2 forced-air warming units (Bair Hugger, Augustine Medical, Inc) set to high (\( \approx 43^\circ \text{C} \)), each attached to an upper-body coverlet that was wrapped into a muff surrounding each forearm and hand. Face warming was achieved by injection of 21 L/min air at \( \approx 42^\circ \text{C} \) at a relative humidity of 100\% into a continuous positive airway pressure mask, which was tightly fitted around the volunteer’s face (Respironics). Air was warmed and humidified with a Vapotherm (Vapotherm, Inc). A central catheter was introduced into the superior vena cava via an antecubital vein and used for cold-fluid infusion. Throughout the study period, mean skin temperature was maintained at \( 31^\circ \text{C} \), excluding the warming sites, by adjusting the temperature of circulating-water (Cincinnati Sub-Zero) and forced-air warmers. Furthermore, the back, upper body, and lower body were individually maintained at the designated skin temperature. On each day of the experiment, core cooling started 20 minutes after arteriovenous shunt vasodilation was documented (defined below). Lactated Ringer’s solution, cooled to \( \approx 4^\circ \text{C} \), was infused at rates sufficient to decrease tympanic membrane temperature \( 1^\circ \text{C/h} \) to \( 2^\circ \text{C/h} \) because these rates are not associated with induction of dynamic thermoregulatory responses.\textsuperscript{7} Fluid was given until the shivering threshold was identified.

Measurements

Heart rate was measured continuously with an ECG; blood pressure was determined oscillometrically at 5-minute intervals at the left ankle. A pulse oximeter continuously determined arterial oxygen saturation.

All temperatures were recorded with Mon-a-therm thermocouples (Malinckrodt Anesthesiology Products, Inc). Core temperature was recorded from the tympanic membrane. Volunteers inserted the aural probe until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected gentle rubbing of the attached wire. The aural canal was occluded with cotton; the probe was securely taped in place; and a gauze bandage was positioned over the external ear. Appropriate placement was confirmed when volunteers easily detected gentle rubbing of the attached wire.

Mean skin surface temperature was determined from 15 area-weighted sites.\textsuperscript{26,27} On the arm-warming day, lower-arm and hand temperatures were excluded from the calculation of mean skin temperature; similarly, facial temperature was excluded from the calculation of mean skin temperature on the face-warming day. Air temperature inside the mask was measured by a thermocouple hanging freely within the mask space, whereas facial skin tempera-

Data Analysis

On each study day, hemodynamic, respiratory, ambient temperature, and relative humidity data were averaged for each volunteer across the cooling period; these values were then averaged for all volunteers. A sustained increase in oxygen consumption (\( \dot{V}_\text{O}_2 \)) of \( \geq 30\% \), as determined by a blinded investigator, identified the shivering threshold. The baseline for this analysis was the steady-state value \( \leq 5\% \) variation in \( \dot{V}_\text{O}_2 \) before core cooling had started.

Results on the 3 study days were compared by use of repeated-measures analysis of variance (ANOVA) and Dunnett’s post hoc tests. Results are expressed as mean \( \pm \) SD; differences were considered statistically significant at \( P<0.05 \).

Results

The volunteers were 28\( \pm \)3 years old, weighed 81\( \pm \)10 kg, and were 175\( \pm \)7 cm tall. One volunteer dropped out of the study after the control and arm-warming days.

Ambient temperature, relative humidity, mean arterial pressure, heart rate, respiratory rate, average end-tidal \( \text{PCO}_2 \), and \( \text{SpO}_2 \) were similar on each study day (Table 1). Mean skin temperature was maintained at \( \approx 31^\circ \text{C} \). Per protocol, all volunteers were vasoconstricted before the cold-fluid infusion started. Air temperature inside the continuous positive airway pressure mask on the face-warming day averaged 38.6\( \pm \)1.4\( ^\circ \text{C} \) (Table 2).

Arm warming reduced the shivering threshold by 0.2\( \pm \)0.3\( ^\circ \text{C} \), from 36.7\( \pm \)0.1\( ^\circ \text{C} \) to 36.5\( \pm \)0.3\( ^\circ \text{C} \). Face warming reduced the shivering threshold by 0.1\( \pm \)0.2\( ^\circ \text{C} \), from 36.7\( \pm \)0.1\( ^\circ \text{C} \) to 36.5\( \pm \)0.3\( ^\circ \text{C} \) (the Figure). The value for ANOVA across all 3 treatments was \( P=0.34 \), so post hoc comparisons were not undertaken. This study achieved a 95\% power to detect a 0.5\( ^\circ \text{C} \) difference between the control threshold and either of the treatment thresholds at \( \alpha=0.05 \).

Discussion

The extent to which induction of core hypothermia will prove therapeutic in stroke victims remains unknown. Results in animals, though, are overwhelmingly positive and indicate that 3\( ^\circ \text{C} \) to 4\( ^\circ \text{C} \) of hypothermia provides better protection than existing pharmacological treatments.\textsuperscript{1,2} Uncontrolled human studies are also encouraging.\textsuperscript{30} Arm or face warming reduced shivering thresholds by only \( \approx 0.2^\circ \text{C} \). Neither of these decreases was statistically significant (although we had 95\% power to detect 0.5\( ^\circ \text{C} \) changes),
and neither decrease was clinically important. Our data thus fail to support the proposal of Iaizzo et al\textsuperscript{15} that “this cooling paradigm holds promise as a means for the induction of mild hypothermia which may enhance cerebral protection in individuals at risk of brain injury.”

The theory behind using cutaneous warming to treat shivering is that both skin and core temperatures contribute to control of thermoregulatory responses. Warming the skin surface reduces the core temperature that triggers shivering. However, skin temperature contributes only 20\% to steady-state control of shivering.\textsuperscript{24,25} Furthermore, the extremities are relatively insensitive to thermal manipulation.\textsuperscript{31,32} Hand temperature in the 2 studies was presumably greater than for the skin surface as whole.\textsuperscript{31,32} The difficulty with using facial warming to ablate shivering is that the surface area of the face is tiny, perhaps only 4.5\% of the total skin area. It thus seems unlikely that facial warming alone would markedly reduce the shivering threshold. The extent to which oropharyngeal and airway thermal receptors contribute to control of shivering remains unknown. However, our results do not suggest that warming facial skin and airway receptors produces clinically important inhibition of shivering.

A critical difference between our study and previous similar ones\textsuperscript{14,15} is that we quantified the shivering threshold rather than simply observing a short-term reduction in shivering intensity. Thus, although Sweney et al\textsuperscript{14} and Iaizzo et al\textsuperscript{15} found that acute application of hand or face warming reduced shivering in nearly normothermic volunteers, we observed only trivial reductions in the steady-state shivering threshold. The most likely explanation is that unlike sustained warming, rapid increases in skin temperature provoke powerful dynamic responses.\textsuperscript{34} Thermoregulatory response thresholds\textsuperscript{35,36} and thermal sensation\textsuperscript{37–39} depend not only on static temperatures but also on the rate at which temperatures change. For example, rapid changes in skin temperature markedly augment cutaneous contribution to the sweating threshold\textsuperscript{35,36} and improve thermal sensation during hyperthermia.\textsuperscript{38} The magnitude of dynamic thermoregulatory response to facial warming remains unknown but may be even greater than for the skin surface as a whole.

Rapid increases in skin temperature ameliorate shivering.\textsuperscript{17–19} A brief reduction in shivering intensity might well facilitate performing a neurological examination, as proposed by Sweney et al.\textsuperscript{14} Nonetheless, therapeutic hypothermia must be maintained for hours or days and thus represents a thermal steady state. Therefore, the steady-state conditions of our study may best represent the typical clinical situation. Our results suggest that neither lower-arm nor face warming will prevent shivering over the period needed for therapeutic hypothermia.

<table>
<thead>
<tr>
<th>TABLE 1. Potential Confounding Factors</th>
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<tr>
<td><strong>Control</strong></td>
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<tr>
<td>Ambient temperature, °C</td>
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<tr>
<td>Relative humidity, %</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
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<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>SPO\textsubscript{2}, %</td>
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<tr>
<td>Respiratory rate, breaths/min</td>
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<tr>
<td>End-tidal PO\textsubscript{2}, mm Hg</td>
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Values were first averaged over the infusion period in individual volunteers and then averaged among the volunteers. Data are presented as mean±SD.

<table>
<thead>
<tr>
<th>TABLE 2. Values at the Shivering Threshold</th>
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<tr>
<td><strong>Control</strong></td>
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<td>Total lactated Ringer’s, L</td>
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<td>Core cooling rate, °C/h</td>
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<tr>
<td>Facial skin temperature, °C</td>
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<td>Arm skin temperature, °C</td>
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<tr>
<td>Mean skin temperature, °C</td>
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<tr>
<td>Shivering threshold, °C</td>
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Data are presented as mean±SD.
Individual values (○) for shivering thresholds on the 3 experimental days. Mean±SD (□) for each day is also indicated. Thresholds did not differ significantly on the 3 treatment days.

Our volunteers were much younger and healthier than stroke victims, and temperature sensitivity is linearly dependent on age, with older people having a reduced cutaneous thermal sensitivity and a reduced thermal perception during cooling. Furthermore, the shivering threshold is reduced a full degree centigrade in the elderly. Inducing tolerance to therapeutic hypothermia is thus likely to be easier in elderly stroke victims than in young volunteers. Nonetheless, our results suggest that cutaneous warming alone will be insufficient and that pharmacological intervention will be required.

Because skin temperature contributes 20% to control of vasoconstriction and shivering, each 1°C decrease in mean skin temperature increases the shivering threshold 0.2°C. Mean skin temperature was kept constant at a low value throughout our study to increase the threshold, thereby minimizing risk from infusion of large amounts of cold fluid.

A limitation of our study is the use of tympanic membrane temperature as an indicator of core body temperature during face warming. Previous work suggests that tympanic membrane temperatures can be artifactually elevated during head or facial skin warming. However, the observed differences between tympanic and esophageal temperatures were tiny. Even small inaccuracies in our temperature measurements would not obviate our major finding that physical warming fails to induce useful amounts of thermoregulatory tolerance.

In summary, we found that neither lower-arm nor facial warming substantially reduces the shivering threshold in unanesthetized volunteers. It thus seems unlikely that either nonpharmacological intervention will contribute meaningfully to induction of therapeutic hypothermia.

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