The Effect of Altering Skin-Surface Cooling Speeds on Vasoconstriction and Shivering Thresholds

Yoshie Taniguchi, MD,† Rainer Lenhardt, MD,‡ Daniel I. Sessler, MD,* and Andrea Kurz, MD*

BACKGROUND: Both core and skin temperatures contribute to steady-state thermoregulatory control. Dynamic thermoregulatory responses trigger aggressive defenses against rapid thermal perturbations. These responses potentially complicate interpretation of thermoregulatory studies and could slow induction of therapeutic hypothermia. We thus tested the hypothesis that rapid external skin-cooling triggers vasoconstriction and shivering at higher mean skin temperatures than slow or moderate rates of skin cooling.

METHODS: Eleven healthy volunteers were cooled at 3 skin-cooling rates using forced air or/and conductive cooling in random order. One day volunteers received slow (∼2°C/h) skin cooling, and on another day, they received both medium (∼4°C/h) and fast (∼6°C/h) skin cooling. An endovascular heat-exchanging catheter maintained core temperature. Fingertip blood flow ≥0.25 mL/min defined onset of vasoconstriction; sustained ≥25% increase in oxygen consumption defined onset of shivering. Results were evaluated with repeated-measures analysis of variance, with P < 0.05 representing statistical significance.

RESULTS: Volunteers were 25 ± 5 years of age (mean ± SD), 175 ± 7 cm tall, and weighed 63 ± 10 kg. Core temperature remained constant (∼37°C) throughout each study day. At vasoconstriction, mean skin temperatures were 33.2°C (95% confidence interval [CI]: 32.0°C, 34.4°C), 33.5°C (95% CI: 32.3°C, 34.7°C), and 33.0°C (95% CI: 31.4°C, 34.6°C) at slow, medium, and fast skin-cooling rates, respectively. Mean skin temperatures at shivering were also comparable: 31.4°C (95% CI: 30.3°C, 32.5°C), 31.5°C (95% CI: 30.2°C, 32.8°C), and 30.7°C (95% CI: 28.9°C, 32.5°C), respectively.

CONCLUSIONS: Onset of vasoconstriction and shivering occurred at similar mean skin temperatures with all 3 cooling rates. Aggressive surface cooling can thus be used in thermoregulatory studies and for induction of therapeutic hypothermia without provoking dynamic thermoregulatory defenses. (Anesth Analg 2011;113:540–4)
Dynamic components potentially complicate at least 2 situations. The first is the conduct and interpretation of thermoregulatory studies. There are several methods of determining the dose-dependent effects of various drugs on thermoregulatory control.\textsuperscript{13–16} The one used most often involves gradually increasing skin and core temperatures until sweating is provoked, followed by gradually reducing temperatures until vasoconstriction and then shivering are observed. The core and skin temperatures that trigger each response are then used to estimate the core temperature that would have triggered the response had mean skin temperature been maintained at some designated level.\textsuperscript{17}

Skin-temperature manipulation in such studies is usually restricted to approximately 2°C/h for fear of triggering dynamic components of the thermoregulatory response that would confound proper interpretation of steady-state thresholds. These studies would be easier, quicker, and safer if skin temperature could be altered more quickly.

A second situation in which dynamic thermoregulatory responses may be important is during induction of therapeutic hypothermia. Therapeutic hypothermia has been shown to ameliorate the effects of neonatal hypoxia\textsuperscript{18,19} and cardiac arrest\textsuperscript{20,21}; however, many investigators believe that hypothermia may also complement other treatments for stroke and acute myocardial infarction. For each indication, it is probably important to rapidly reduce core temperature for optimal effect. One approach is to directly cool the core using an endovascular heat-exchanging catheter\textsuperscript{22}; the principal alternative approach is skin-surface cooling.\textsuperscript{23} But to the extent that rapid surface cooling provokes dynamic thermoregulatory defenses, skin cooling will provoke vasoconstriction and shivering and the associated hemodynamic and autonomic perturbations at higher temperatures than would otherwise be expected, thus impeding induction of hypothermia.

It is thus of considerable interest to determine whether surface cooling over a range of clinically practical rates in fact triggers dynamic thermoregulatory defenses. We therefore tested the hypothesis that rapid external skin cooling (≥6°C/h) triggers vasoconstriction and shivering at higher mean skin temperatures than moderate (≥4°C/h) or slow (≥2°C/h) rates of skin cooling in healthy volunteers.

**METHODS**

With approval of the Committee on Human Research at the University of Bern and written informed consent, 11 healthy volunteers were enrolled. Exclusion criteria included obesity (body mass index ≥35 kg/m\textsuperscript{2}); premedication (including oral contraceptives); pregnancy; recent fever; height <150 cm; smoking of >5 cigarettes per day; or history of diabetes, thyroid disease, dysautonomia, Raynaud syndrome, coagulopathy, or neuromuscular disease.

**Protocol**

Volunteers fasted and refrained from smoking 8 hours before each study day. Studies started at approximately 8:00 AM. On both days, the volunteers were kept comfortably warm during the study setup to ensure peripheral arteriovenous shunt vasodilatation.

Volunteers were randomly assigned to receive 3 different skin-surface cooling rates over 2 days: on one day, mean skin temperature (as described below) was reduced at a rate of ≈2°C/h (slow cooling). On the alternate day, volunteers randomly received skin-surface cooling at rates of ≈4°C/h (medium cooling) and ≈6°C/h (fast cooling). After confirming the shivering threshold, the volunteers were rewarmed until arteriovenous shunt vasodilatation could be confirmed and maintained for 30 minutes. Subsequently, cooling was restarted at the alternate cooling rate. Skin cooling ended (for all 3 cooling rates) when shivering was detected.

The order of the study days and the order of the medium and fast cooling rates were randomly assigned, based on computer-generated codes. Skin-surface temperature was manipulated with forced air (Polar Air Model 600; Arizant Medical, Inc., Eden Prairie, MN) and/or an Allon circulating-water garment system (MTRE Advanced Technologies, Ltd., Tel Aviv, Israel) or a Medi-Therm II circulating-water mattress (Nufer Medical, Gümligen, Switzerland). Ambient operating room temperature was maintained at 26.6°C ± 1.0°C.

During the entire study, core temperature was maintained stable at the volunteers’ initial (prestudy) core temperature with an Alsius endovascular temperature-management catheter (Icy; Alsius Medical Corp., Irvine, CA). This catheter is a single-use, heparin-coated 8.5F 38-cm central line with a single infusion lumen and a 24-cm-long heat-exchange element. With the volunteers under slight propofol sedation (1–2 mg/kg), we injected local anesthesia and inserted the catheter into the vena cava via a femoral vein. The ipsilateral femoral vein was used on the second study day. The catheter’s 3 balloons were perfused with sterile saline in a closed-loop system by a perfusion system (CoolGard 3000 Thermal Regulation System; Alsius Medical Corp.), which automatically adjusts the temperature of the perfusate between 0°C and 42°C to maintain baseline core temperature throughout the study.

After catheter insertion, we waited for approximately 45 minutes to ensure that there was no propofol effect on the dynamic component of thermoregulatory response before the different skin-cooling manipulations were started.

**Measurements**

Morphometric and demographic characteristics were recorded. Baseline values were recorded 15 minutes before thermal manipulation. Oscillometric arterial blood pressure and heart rate were recorded at 5-minute intervals throughout the study.

To measure area-weighted skin-surface temperature, Mon-a-thermocouples (Tyco-Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO) were attached to 15 sites.\textsuperscript{24} Core temperature was measured with Mon-a-thermocouples that were positioned adjacent to the tympanic membrane by the participant; appropriate placement was confirmed when a gentle rubbing of the attached wire could easily be detected. The aural canal was then occluded with cotton and the thermocouple taped in place. All thermocouples were connected to a calibrated Iso-Thermex 16-channel thermocouple thermometer (Columbus Instruments International, Corp., Columbus, OH). Temperatures were measured at 2-second intervals, averaged over a
Skin-Surface Cooling Speed and Thermoregulatory Responses

**Table 1. Study Variables at Baseline, Vasoconstriction, and Shivering**

<table>
<thead>
<tr>
<th></th>
<th>Slow</th>
<th>Medium</th>
<th>Fast</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin-cooling rate (°C/h)</td>
<td>2.1 (2.0, 2.2)</td>
<td>3.8 (3.4, 4.2)</td>
<td>6.2 (5.2, 7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ambient temperature (°C)</td>
<td>26.0 (25.2, 26.8)</td>
<td>27.0 (26.1, 27.9)</td>
<td>26.6 (26.1, 27.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>88 (79, 97)</td>
<td>89 (83, 95)</td>
<td>92 (83, 101)</td>
<td>0.69</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.6 (36.4, 36.8)</td>
<td>36.7 (36.5, 36.9)</td>
<td>36.7 (36.5, 36.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean skin temperature (°C)</td>
<td>33.2 (32.0, 34.4)</td>
<td>33.5 (32.3, 34.7)</td>
<td>33.0 (31.4, 34.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Time to onset (min)</td>
<td>53 (30, 93)</td>
<td>31 (17, 54)</td>
<td>18 (10, 31)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>88 (78, 98)</td>
<td>89 (82, 96)</td>
<td>91 (79, 103)</td>
<td>0.88</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>58 (49, 67)</td>
<td>66 (59, 73)</td>
<td>63 (53, 73)</td>
<td>0.22</td>
</tr>
<tr>
<td>Shivering</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.6 (36.4, 36.8)</td>
<td>36.6 (36.4, 36.8)</td>
<td>36.7 (36.5, 36.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean skin temperature (°C)</td>
<td>31.4 (30.3, 32.5)</td>
<td>31.5 (30.2, 32.8)</td>
<td>30.7 (28.9, 32.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Time to onset (min)*</td>
<td>114 (80, 162)</td>
<td>60 (42, 85)</td>
<td>41 (29, 58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>93 (85, 101)</td>
<td>87 (77, 97)</td>
<td>96 (85, 107)</td>
<td>0.26</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 (56, 72)</td>
<td>64 (55, 73)</td>
<td>62 (55, 69)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Results presented as mean (99% confidence interval).  
* Time to onset presented as median (99% confidence interval).

**Figure 1.** Core and mean skin temperatures as a function of time. MST: 2 = mean skin temperature during cooling at a rate of 2°C/h; MST: 4 = mean skin temperature during cooling at a rate of 4°C/h; MST: 6 = mean skin temperature during cooling at a rate of 6°C/h. Data are given as mean ± SD.

Volunteers weighed 63 ± 10 kg. As shown in Table 1, skin-cooling rates were 2.1°C ± 0.1°C/h, 3.8°C ± 0.5°C/h, and 6.2°C ± 1.3°C/h. Regardless of the cooling rate, core temperatures remained essentially constant (~37°C) at both vasoconstriction and shivering thresholds (Table 1, Fig. 1).

Mean skin temperatures at the beginning of the study were not statistically different on both days and for all treatments (Table 1). Mean skin temperatures at vasoconstriction were 33.2°C (95% confidence interval [CI]: 32.0°C, 34.4°C), 33.5°C (95% CI: 32.3°C, 34.7°C), and 33.0°C (95% CI: 31.4°C, 34.6°C) (P = 0.79) at slow, medium, and fast rates of skin cooling, respectively. Mean skin temperatures at the shivering threshold were also not statistically significantly different at each skin-cooling rate: 31.4°C (95% CI: 30.3°C, 32.5°C), 31.5°C (95% CI: 30.2°C, 32.8°C), and 30.7°C (95% CI: 28.9°C, 32.5°C) (P = 0.53) for slow, medium, and fast rates, respectively. Thus, mean skin temperatures were similar at vasoconstriction regardless of cooling rate. Likewise, mean skin temperatures at shivering were within 0.5°C at all cooling rates and lower than temperatures at vasoconstriction (Table 1).

**RESULTS**

Volunteers were 25 ± 5 years of age, 175 ± 7 cm tall, and weighed 63 ± 10 kg. As shown in Table 1, sample size analysis indicated that 11 volunteers provided 90% power for identifying a statistically significant mean difference of 0.35°C between study days, assuming a within-volunteer standard deviation of 0.25°C and a 2-tailed significance criterion of 0.01.

**Sample Size Considerations**

Sample size analysis indicated that 11 volunteers provided a statistical power of 90% for identifying a statistically significant mean difference of 0.35°C between study days, assuming a within-volunteer standard deviation of 0.25°C and a 2-tailed significance criterion of 0.01.

5-minute period, and recorded. Measurements had an accuracy of 0.1°C and a precision of 0.01°C.

Vasoconstriction was assessed by volume plethysmography at 5-minute intervals, which is the most reliable measure of fingertip (i.e., arteriovenous shunt) blood flow. Thermoregulatory shivering was evaluated by indirect calorimetry, because oxygen consumption is the best overall representation of integrated metabolic rate. The metabolic monitor (Vmax; SensorMedics Corp., Yorba Linda, CA) was used in canopy mode on both study days and provided measurements with an absolute accuracy of 5% to 10%. Measurements were averaged over 1-minute intervals and recorded at 5-minute intervals.

**Data Analysis**

Ambient temperature was averaged for each volunteer, and resulting values were then averaged among all volunteers. In previous studies, thermoregulatory response thresholds were determined from both core and mean skin temperatures, but in this study, core temperature was kept constant. Our primary outcome was thus the mean skin temperatures that triggered vasoconstriction and shivering. Vasoconstriction was defined as sustained fingertip blood flow <0.25 mL/min, and shivering was defined by a sustained ≥25% increase in oxygen consumption.

Results for each study day were compared using repeated-measures analysis of variance and Scheffé F tests. Results were expressed as mean ± SD, and mean and confidence intervals; differences were considered significant at P < 0.01.
rates of skin cooling, respectively (Fig. 1). Times to shivering onset were also different: 114 minutes (80, 162 minutes), 60 minutes (42, 85 minutes), and 41 minutes (29, 58 minutes) ($P < 0.0001$) for slow, medium, and fast rates, respectively. Onset of vasoconstriction and shivering was achieved most rapidly at the fastest skin-cooling rate (Table 1, Fig. 1).

**DISCUSSION**

The extent to which dynamic responses to rapid core- and skin-temperature changes potentially complicate thermoregulatory studies and induction of therapeutic hypothermia is of considerable physiological and clinical interest. However, the ability to perform such studies in humans has been limited because it is difficult to independently manipulate core and skin temperatures.

With sufficient attention to detail, it is possible to clamp mean skin temperature using either water immersion or a combination of forced air and circulating water. However, it is then difficult to increase or decrease core temperature. One strategy has been to increase core temperature by having volunteers exercise, but this approach is suboptimal because exercise per se reduces the sweating threshold, thus confounding the results. As early as 1959, investigators tried to independently cool the core by having volunteers ingest an ice and water slurry. However, the method is obviously impractical in many clinical situations (i.e., during anesthesia or in critically ill patients) and, at best, produces only a modest degree of hypothermia. More recently, gastric and bladder lavage have been attempted, but proved respectively impractical and ineffective.

Our study was possible because we were able to clamp core temperature using 1 of 3 recently developed endovascular heat-exchanging catheters. This allowed us to independently cool the skin surface without consequent changes in core temperature. (The core response to surface warming or cooling depends on thermoregulatory status, body heat content, and degree of cooling stress; however, the normal consequence is a compensatory opposite change in core temperature.) The endovascular system we used was effective at maintaining normothermia; core temperatures were thus virtually identical at vasoconstriction and shivering at each skin-cooling rate. The mean skin temperatures triggering each response could therefore be directly compared.

Our primary result is that the mean skin temperature triggering vasoconstriction was similar at skin-cooling rates ranging from approximately 2°C/h to 6°C/h; the skin temperatures triggering shivering were lower than those at vasoconstriction, but again similar at each cooling rate. At least within this factor-of-3 range of cutaneous cooling rates, thermoregulatory response can be considered a pseudo–steady-state. Our results indicate that skin-cooling rates in thermoregulatory investigations no longer need be restricted to $\approx 2°C/h$, but can instead be increased to $6°C/h$, which will facilitate and speed the studies. The extent to which this information will speed studies is indicated by the onset times for vasoconstriction and shivering, which decreased by nearly a factor of 3 in our volunteers.

Perhaps more importantly, our results indicate that skin-cooling rates up to 6°C/h can be used during induction of therapeutic hypothermia without increasing the requirement for drugs that induce partial thermoregulatory tolerance. Being able to cool quickly from the skin surface without provoking dynamic thermoregulatory compensations is clinically important for 2 reasons. The first is that vasoconstriction and shivering are themselves potentially harmful in fragile patients. The second is that they are each effective, thus substantially slowing the rate of core cooling.

We used a combination of circulating water and forced air to reduce skin temperature, and $\approx 6°C/h$ was about the fastest decrease we could obtain. (Animal studies have compared responses to skin cooling at rates between 14°C/h and 140°C/h, but these results are difficult to extrapolate to humans.) However, immersion in cool water certainly reduces mean skin temperature far $\approx 6°C/h$ and newer hypothermia devices probably will as well. It remains probable that yet faster cooling rates will indeed provoke dynamic thermoregulatory responses. Availability of a new generation of endovascular heat-exchange catheters that can cool the core of adult humans as fast as $10°C/h$ will also allow investigators to determine the relative contributions of dynamic and steady-state thermoregulatory defenses as a function of the core cooling rate.

In summary, onset of vasoconstriction and shivering occurred at similar mean skin temperatures when the skin was cooled at between 2°C/h and 6°C/h. Surface cooling at a rate of $\approx 6°C/h$ can thus be used in thermoregulatory studies and for induction of therapeutic hypothermia without provoking dynamic thermoregulatory defenses.

**DISCLOSURES**

Name: Daniel I. Sessler, MD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Daniel I. Sessler has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yoshie Taniguchi, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Yoshie Taniguchi has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Rainer Lenhardt, MD.
Contribution: This author helped design the study.
Attestation: Rainer Lenhardt has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Andrea Kurz, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Andrea Kurz has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**ACKNOWLEDGMENTS**

We thank Gilbert Haugh, MS, for the statistical analysis and Nancy L. Alsip, PhD, for editorial assistance (Center for Clinical Research Services & Support at the University of Louisville).
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