Recovery from mild hypothermia can be accelerated by mechanically distending blood vessels in the hand

DENNIS GRAHN, DONALD E. WATENPAUGH, AND H. CRAIG HELLER
Departments of Biological Sciences and Anesthesiology, School of Medicine, Stanford University, Stanford, California 94305; and Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas 76107

Grahn, Dennis, J ohn G. Brock-Utne, Donald E. Watenpaugh, and H. Craig Heller. Recovery from mild hypothermia can be accelerated by mechanically distending blood vessels in the hand. J. Appl. Physiol. 85(5): 1643–1648, 1998.—Peripheral vasoconstriction decreases thermal conductance of hypothermic individuals, making it difficult to transfer externally applied heat to the body core. We hypothesized that increasing blood flow to the skin of a hypothermic individual would enhance the transfer of exogenous heat to the body core, thereby increasing the rate of rewarming. External auditory meatus temperature (T _{e_{\text{m}}}) was monitored in hypothermic subjects during recovery from general anesthesia. In 10 subjects, heat (45–46°C, water-perfused blanket) was applied to a single forearm and hand that had been placed in a subatmospheric pressure environment (−30 to −40 mmHg) to distend the blood vessels. Heat alone was applied to control subjects (n = 6). The application of subatmospheric pressure resulted in a 10-fold increase in rewarming rates as determined by changes in T _{e_{\text{m}}} [13.6 ± 2.1 (SE) °C/h in the experimental group vs. 1.4 ± 0.1 °C/h in the control group; P < 0.001]. In the experimental subjects, the rate of change of T _{e_{\text{m}}} decreased sharply as T _{e_{\text{m}}} neared the normothermic range.

Like all homeothermic mammals, humans maintain a relatively constant core body temperature (T _{c}). Mammals minimize the energy costs of homeothermy by selecting thermal environments in which T _{c} can be maintained with minimal metabolic effort. Within this thermoneutral environment, T _{c} is regulated by vasomotor adjustments that control heat transfer between the body core and the skin (2). Vasoconstriction reduces heat transfer; vasodilation increases heat transfer. Vasomotor tone is centrally regulated and determined primarily by T _{c} (33, 34). When vasomotor responses are not sufficient to maintain a desired T _{c}, metabolically more expensive thermogenic or thermolytic mechanisms are activated.

Hypothermia occurs when the capacity to conserve and produce heat is overwhelmed by environmental cold or is compromised (e.g., by anesthesia) (19). Because vasoconstriction occurs before the activation of thermogenic mechanisms, hypothermia in conscious individuals is always associated with maximal vasoconstriction. Whereas vasoconstriction is an appropriate response to prevent heat loss from the thermal core, it also slows the transfer of exogenous heat from the body surface to the body core (5). Thus application of heat to the skin of a hypothermic individual affects T _{c} slowly. It follows that removal of the vasoconstrictive blockade to heat exchange would facilitate transfer of heat from the skin to the body core in hypothermic individuals. The purpose of this study was to determine to what extent heat transfer to the thermal core of a hypothermic individual could be enhanced by increasing blood flow through the skin area to which exogenous heat is applied.

Blood volume and blood flow in an appendage can be altered by placing the appendage in a sealed enclosure and manipulating the local atmospheric pressure. Blood vessels in the hand can be distended by exposing the distal portion of the limb to subatmospheric pressures (14). The application of superficial heat to the mechanically distended tissues increases blood flow through the hand (4). Therefore, we hypothesized that the combined application of subatmospheric pressure and heat to the hand of a hypothermic individual would increase subcutaneous blood flow and thus be an effective noninvasive technique for rapidly transferring heat from the skin surface to the body core.

MATERIALS AND METHODS

Subjects. This study was conducted in the Post Anesthetic Care Unit (PACU) of Stanford University Hospital and followed a protocol approved by the Human Subjects Committee of Stanford University. Informed consent for participation in this study was obtained from 32 patients undergoing a variety of surgical procedures, before the induction of anesthesia. The axillary temperature of the potential subjects was measured on admission to the PACU. Sixteen subjects (age range 21–77 yr, mean age 46.7 yr; 9 men, 7 women) qualified as mildly hypothermic (33.5°C < axillary temperature < 35.5°C) and were randomly assigned to either the experimental or control group.

Equipment. The experimental device consisted of a circulating water bath, a vacuum pump, and a sealed chamber that housed a water-perfusion blanket. The chamber was constructed from a 35-cm length of acrylic tubing (15.25 cm ID, 3 mm thick) capped at one end with an acrylic plate. A conical neoprene collar (15 cm long, 16–8 cm OD, 6 mm thick) created a seal around the subject’s forearm. An acrylic adapter ring (7 cm long, 16 cm OD, 5 mm thick) connected the chamber body to the neoprene collar. The chamber was connected to the vacuum pump via a port in the chamber wall and polyethylene tubing (1/4 in. ID, 1/8 in. wall). Water lines (polyethylene tubing, 1/4 in. ID, 1/16-in. wall) connecting the water bath to the water-perfusion blanket were attached by means of compression fittings through holes in the adapter ring. Chamber pressure was measured with an analog pressure gauge (range 0 to −100 mmHg). Chamber pressure was controlled by adjusting a needle valve mounted in the vacuum line. Temperatures were measured with copper-constantan thermo-
couples connected to custom-made signal-conditioning units with digital temperature displays. Water-perfusion blanket temperature was monitored by measuring the temperature in the water-perfusion line where it entered the vacuum chamber and was controlled by adjusting the temperature of the water bath.

A temperature probe, similar in design to that described by Sato et al. for measuring tympanic membrane temperature in unanesthetized individuals, was used in this study. However, because the temperature probe was placed on our subjects as they were emerging from a surgical plane of anesthesia and there is a substantial risk of perforating the tympanic membrane when a temperature probe is placed directly on the tympanic membrane of an anesthetized individual, tympanic membrane temperature itself was not measured in this study. Instead, external auditory meatus temperature (TEAM) was monitored throughout the experiments. The thermocouple used to measure TEAM was inserted through the center of a sound-attenuation ear plug (Bilsom PERFIL, Billeholmen, Sweden) so that the tip of the thermocouple extended 5 mm past the end of the ear plug. The ear plug was positioned so that the tip of the thermocouple penetrated ~7 mm into the external auditory meatus. TEAM was recorded at ~1-min intervals, and the data were manually entered into a computer for subsequent analyses.

Experimental procedure. Each experiment was initiated after the patient had been admitted to the PACU and the PACU nursing staff had determined that, aside from being hypothermic, the patient was in stable condition (generally 15–30 min after admission to the PACU). The subject was fitted with the device so that the water-perfusion blanket surrounded the forearm, hand, and fingers of a single appendage. For the experimental group (n = 10), the water blanket was maintained at 44–46°C, and the chamber was evacuated to a pressure of ~30 to ~40 mmHg. For two of the six control subjects, the water-perfusion blanket was maintained at 44–46°C, but the chamber was not evacuated. The other four subjects included in the control group received conventional PACU treatment (two were wrapped in warm blankets and two were subjected to forced-air rewarming techniques).

Data analysis. TEAM vs. time graphs were generated for each subject. Visual inspection of the graphs determined that the experimental subjects' plots were exponentially saturating, whereas those of the control subjects were linear. Because the objective of this study was to determine the effect of treatment on the rate of recovery from hypothermia, the rates of change in TEAM over time, rather than the absolute temperatures, were the relevant measurements. For each subject, the stable TEAM after rewarming served as a baseline. The recorded TEAM values were subtracted from the baseline TEAM to generate return to baseline curves. These curves were then aligned by visually adjusting the time-axis location of the individual plots to maximize the overlap between the individual records. Mean and SE values for the aligned data sets were then calculated at 2-min intervals for the experimental group and at 5-min intervals for the control group. Maximum rewarming rate, the slope of the steepest portion of the TEAM vs. time curves, was calculated for each individual. Mean and SE values for maximum rewarming rates were then calculated for the experimental and control groups. The maximum rewarming rates, initial TEAM, final TEAM, and rewarming time were statistically analyzed by using Student's t-test (P < 0.001). The results from this study were compared with results from previously published studies that assessed the efficacy of other noninvasive rewarming techniques for the treatment of hypothermia.

RESULTS

All subjects were hypothermic (TEAM < 35.5°C) at the onset of treatment (34.6 ± 0.8 (SE) °C) (Table 1). The initial TEAM of the experimental group was not significantly different from that of the control group (34.3 ± 0.9 vs. 34.8 ± 0.3°C). Final temperatures were also not statistically different (36.0 ± 0.5 vs. 36.2 ± 0.4°C, respectively). However, the time required to achieve the final stable TEAM was significantly reduced in the experimental group (8.1 ± 2.3 vs. 59.0 ± 14.3 min, respectively).

The combined application of heat and subatmospheric pressure to a single forearm, hand, and fingers accelerated recovery from hypothermia (Fig. 1). In the experimental subjects, there was an upward inflection of TEAM on application of heat and subatmospheric pressure, but as TEAM approached normal, the rate of change in TEAM decreased. In all of the experimental subjects, the changes in TEAM were complete within 15 min of application of subatmospheric pressure and heat (Fig. 2, top). In contrast, none of the control subjects exhibited an abrupt increase in TEAM (Fig. 2, bottom).

Within the treatment groups, the changes in TEAM over time of the individual subjects were similar. Standardized rewarming curves were generated for the experimental and control groups (Fig. 3). The maximum rate of change of TEAM (the steepest portion of the rewarming curve) of the experimental group was 13.6 ± 2.1°C/h, 10 times faster than that of the control group (1.4 ± 0.1°C/h). The rewarming rates determined in this study are compared with those from comparable studies reported in the literature (see Table 2).

DISCUSSION

A criterion for an effective heating device is that the heat generated by the device reach the desired target. Table 1. Effect on recovery time of mechanically distending subcutaneous vascular during application of heat to the hand of mildly hypothermic individuals

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Initial TEAM, °C</td>
<td>34.3 ± 0.9</td>
<td>34.8 ± 0.3</td>
</tr>
<tr>
<td>Final TEAM, °C</td>
<td>36.0 ± 0.5</td>
<td>36.2 ± 0.4</td>
</tr>
<tr>
<td>Time to final TEAM, min</td>
<td>6.1 ± 2.3*</td>
<td>59.0 ± 14.3</td>
</tr>
</tbody>
</table>

Values are means ± SE for n subjects. Experimental subjects were treated with subatmospheric pressure and heat, whereas control group subjects were treated with conventional noninvasive rewarming techniques or with heat but not with subatmospheric pressure. Experimental subjects received heat applied directly to the skin of a single forearm and hand of an appendage placed in a subatmospheric pressure environment. Subjects were patients recovering from general anesthesia in the Post Anesthetic Care Unit (PACU) and deemed by the PACU nursing staff to be suffering from anesthesia-induced hypothermia. TEAM, external auditory meatus temperature. Initial TEAM, team at the initiation of treatment. *Significantly different from control group (P < 0.001).
Because hypothermia is a condition in which the thermal core of the body falls below the desired temperature range, the thermal core (rather than the peripheral tissues) must be heated to reverse hypothermia. The thermal core is defined as the internal regions of the body having temperatures that are not changed in their relationship to each other by circulatory adjustments or changes in heat dissipation to the environment that affect the thermal shell of the body (19). The thermal core comprises <8% of the total body mass (1). This small central portion of the total body mass needs to be warmed to reverse hypothermia. Thus, to rapidly treat hypothermia, it is necessary to maximize the transfer of heat from the body surface into the thermal core. Blood flow between the body surface and the thermal core is the normal modality for heat transfer between the environment and the body core. However, in hypothermic individuals, vasoconstriction suppresses peripheral blood flow and slows heat transfer between the skin surface and the thermal core. To utilize the circulatory system of a hypothermic individual as a heat-transfer medium, two factors must be considered: 1) peripheral vasoconstriction is centrally mediated, and thus local application of heat to the skin surface will have little effect on vasomotor tone when $T_c$ is below the desired range; and 2) only limited areas of the skin surface are specialized for heat transfer between the body core and the environment.

Thermoregulation is under central nervous system control. The central nervous system receives inputs from temperature sensors located in the body core as well as on the skin surface. A hierarchy of the thermal inputs to the thermoregulatory control system can be determined based on the response to local temperature manipulations. The temperature of the preoptic/anterior hypothalamic region of the brain stem (POAH) is known to provide potent input to the mammalian thermoregulatory system, whereas local skin temperatures provide a relatively low-priority input (28). Local manipulations of POAH temperature ($T_{POAH}$) in experimental mammals activate appropriate thermoregulatory-effector mechanisms: increases in $T_{POAH}$ elicit peripheral vasodilation and active thermolytic responses such as panting and sweating, which decrease $T_c$, whereas decreases in $T_{POAH}$ elicit peripheral vasoconstriction and active thermogenic responses (e.g., shivering), which increase $T_c$ (16). Skin temperature, although important for behavioral thermoregulatory responses, has little impact on autonomic thermoregulatory function (17, 21). Cutaneous thermal input can alter the $T_{POAH}$ thresholds for eliciting metabolic thermoregulatory responses but does not affect the relationship between the displacement of $T_{POAH}$ from the threshold temperature and the magnitude of the thermoregulatory response (17). In fact, eliminating input from the trunk and face cutaneous thermoreceptors (by sectioning nerves supplying the cutaneous receptors)...
METHODS for a detailed description of standardization procedure.

vasoconstrictive blockade to heat transfer.

over warm input from skin sensors, thus preserving the brain to the thermoregulatory system take priority.

animals is in the hypothermic range, warming of the skin is relatively ineffective in reducing shivering or

thermoneutral environment, heat production is relatively constant, and $T_c$ is regulated by controlling heat exchange vasculature. The heat-exchange vasculature is limited to the hairless regions of the face, ears, hands, and feet (13). The heat-transfer structures consist of subcutaneous venous plexuses (dense networks of thin-walled, large-diameter venules) and arteriovenous anastomoses (AVAs) (vascular communications directly between the arteries and the venous plexuses). Where found, these exchange structures are dense, e.g., >500 AVAs/cm² in the nail beds of the fingers and toes (13). The dimensions of venous plexuses determine the blood volume capacity of a heat-exchange region, and the AVAs control the blood flow through the venous plexuses. The blood-flow velocities through the venous plexuses can range from 0.1 to 1 m/s (3). It has been estimated that, with maximum vasodilatation, blood flow into the subcutaneous venous plexuses can be as great as 30% of the total cardiac output (15). Thus when these structures are vasodilated, there is a free exchange of heat between the body core and the environment. We speculate that, in this study, the mechanical distension of the heat-exchange structures filled the venous plexuses to near capacity so that, when the AVAs opened, there was an extremely high blood flow through the venous plexuses in the hand. The heated blood then was returned directly to the thermal core, providing for rapid heat exchange between the treated skin surface and the body core.

The rewarming rates reported here for the control subjects are consistent with the values reported by others using noninvasive rewarming techniques to reverse hypothermia, such as immersing the subject in warm water, wrapping the subject in warmed cotton or water-perfusion blankets, radiant heating, or forcing warm air over the skin surface (see Table 2). These conventional techniques are effective for heating the skin. Unfortunately, because hypothermic individuals are also vasoconstricted, the heat applied to the skin is slow to penetrate into the body core (5). In contrast, by applying heat to mechanically distended heat-exchange vasculature, the applied heat goes directly to the heart, where it is distributed to tissues based on the priority determined by the individual's thermoregulatory system. By accessing the thermal core through the heat-exchange vasculature, the critical core regions (which are normally protected by vasomotor tone) are the first, rather than the last, to receive the superfi-cially applied heat. Because the peripheral thermoregulatory vasoconstriction is reversed when the thermal core, hence the POAH, reaches normothermia, the

Table 2. Comparison of rewarming rates of hypothermic subjects with noninvasive rewarming methods: subatmospheric pressure and heat vs. standard methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Rewarming Rates, °C/h</th>
<th>References</th>
</tr>
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<tr>
<td>Present study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subatmospheric pressure and heat</td>
<td>13.6 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Standard methods</td>
<td>1.4 ± 0.1</td>
<td></td>
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<tr>
<td>Previous studies using standard methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia-induced hypothermia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical patients</td>
<td>0.2–1.4</td>
<td>5, 18, 20, 23, 24, 26, 30</td>
</tr>
<tr>
<td>Volunteers</td>
<td>1.0–1.5</td>
<td>25</td>
</tr>
<tr>
<td>Cold-exposure hypothermia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical patients</td>
<td>1.0–2.4</td>
<td>22, 29</td>
</tr>
<tr>
<td>Volunteers</td>
<td>0.4–3.3</td>
<td>8–12</td>
</tr>
</tbody>
</table>

Values for present study are rate of change in $T_{\text{EAM}}$ (means ± SE). Values for previous studies are range of rewarming rate means reported in cited references. In studies with clinical patients, temperature recording sites varied considerably. One or more of the following temperatures were measured in the clinical studies: tympanic membrane, oral, pulmonary artery, bladder, nasopharynx, or rectal. Tympanic membrane temperatures were measured in anesthesia-induced hypothermia volunteers. Esophageal temperatures were measured in cold-exposure hypothermia volunteers. Standard rewarming methods included forced heated air onto exposed surfaces of the patient, covering patient in warm cotton blankets, patient inhaling heated humidified gases, and application of radiant heat to patient. Forced warm air devices used in the clinical studies delivered air to less than one-half of total body surface. Cold-exposed volunteer subject studies conducted by Giesbrecht and colleagues (8–11) utilized a variety of perturbations during rewarming, including exercise, shivering, inhibition of shivering, and placing the hypothermic individual in an air-circulating chamber in which warm air (46–48°C) was passed over entire body surface.
rapid rise in $T_c$ effected by the method described in this paper is self-regulating and presents little danger of inducing hyperthermia.

Afterdrop, when deep $T_c$ continues to decrease despite the application of heat to the skin surface, is commonly observed during the treatment of hypothermia (7, 32). However, no afterdrop was observed in any of our study subjects. Two factors that determine the incidence and severity of afterdrop are 1) the pattern of cooling and 2) the time delay between cooling and rewarming. Afterdrop is more common after abruptly acquired hypothermia (e.g., accidental immersion in very cold water) than after slowly acquired hypothermia (prolonged exposure to mild cold) (32). Increasing the delay between cooling and treatment onset decreases the incidence of afterdrop observed during treatment (32). The absence of afterdrop in our study is not surprising because the hypothermia was slowly acquired in our subjects and there was a considerable lag between the time when the subjects began to lose heat and when rewarming treatment was commenced.

Conventional wisdom suggests that afterdrop is the result of cold blood returning to the core from the arms and legs where surface rewarming has caused peripheral vasodilation. However, this circulatory explanation of afterdrop is unlikely because peripheral blood flow remains low during afterdrop (32). An alternative explanation of the afterdrop phenomenon is based on physical conduction of heat through tissue. When the surface of a mass of tissue is cooled, a thermal gradient is established between the surface and the deep core of the mass, with each layer of the tissue cooling as the layer exterior to it extracts heat from it. Once a thermal gradient has been established and a direction of temperature change has been initiated, a reversal of the heat flux through the surface does not immediately affect the deeper layers of tissue, and the established cooling pattern continues. Webb (32) states: “To avoid afterdrop, one must heat the core organs first: e.g., by heating the blood in an extracorporeal circuit or by using peritoneal lavage or diathermy.” The device used in the present study simulates an extracorporeal heating circuit except that it heats the blood in a noninvasive manner. It is anticipated that, if a device similar to that described here were applied to victims of rapidly acquired hypothermia immediately after cold exposure, afterdrop would be either eliminated or greatly attenuated.

A controversy in thermoregulatory physiology is whether tympanic membrane temperature is an accurate measurement of $T_c$ in humans. The argument against tympanic membrane temperature as a measurement of $T_c$ is that tympanic membrane temperature in part measures skin $T_{EAM}$ and thus, because tympanic membrane temperature can be influenced by the skin temperature of the face and neck, it is in fact a measurement of peripheral temperature. However, when the external auditory meatus was sealed, isolating the internal portion of the meatus from ambient conditions, thermal manipulations of the scalp and face had little effect on tympanic membrane temperature, and tympanic membrane temperature was virtually indistinguishable from esophageal temperatures (27). When both feet were heated in a water bath, esophageal and tympanic membrane temperatures responded in a similar manner. Actually, the appearance of a temperature transient on foot warming was slightly faster in tympanic membrane than in esophageal temperature (27). Esophageal temperature was not measured in this study for practical reasons: under the best conditions, most patients refused placement of an esophageal probe, and it was unreasonable to expect our patient subject population to accept placement of an esophageal probe as they were emerging from anesthesia after an invasive surgical procedure. However, we can see no reason to doubt that the same close correlation between tympanic membrane and esophageal temperatures as reported by Sato et al. (27) would be seen under the conditions of our study. Deviations between esophageal and tympanic membrane temperatures are more commonly seen in studies involving exercise or exposure to thermal transients (6), neither of which were characteristics of our study.

In the present study, relative change in the recorded temperature was the relevant measurement. The thermocouple was placed in the external auditory meatus internal to the body surface and isolated from ambient temperature influences by the ear plug. The skull and overlying tissues serve as an insulation barrier between the brain and the environment, and thus a thermal gradient exists along the external auditory meatus in which temperatures range from close to ambient temperature at the ear pinna to near the temperature of the thermal core at the tympanic membrane. The position of the tip of the thermocouple in the ear canal determined the extent to which changes in local ambient temperature could have influenced the measured temperature. However, because ambient temperature remained constant, the ear plug isolated the tip of the temperature probe from the external environment, and the recording site was fixed, the relative changes in the measured temperatures reflected changes in the subjects’ internal thermal milieu rather than the effect of changes in local external thermal conditions. It may be that, because tympanic membrane temperature itself was not measured, the observed changes in the measured temperature underestimated the true $T_c$ response, but they are still accurate reflections of rates of change of $T_c$.

The authors express gratitude to the PACU nursing staff and the operating room personnel whose cooperation made this project possible, to James Roundy for assistance in data collection, and to Grace Hagiwara for critical input during the preparation of this manuscript.

A patent has been issued for a device [D. Grahn (Inventor); Stanford University (Assignee). Apparatus and Method for Core Rewarming of Mammals Experiencing Hypothermia. US Patent 5,683,438. 4 Nov. 1997] and Stanford Univ. has entered into a licensing agreement with Aquarius Medical Corp., Scottsdale, AZ, for the commercialization of the technology. Included in the license is a royalties agreement that grants Stanford Univ. a percentage of the net sales of the technology, which will be shared by the University
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and the inventor. D. Grahn is also serving as a consultant to Aquarius Medical Corp. to assist in the development of the technology.

Address for reprint requests: D. Grahn, Dept. of Biological Sciences, Stanford Univ., Stanford, CA 94305 (E-mail: dagrahn@leland.stanford.edu).

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