Inhibition of shivering increases core temperature afterdrop and attenuates rewarming in hypothermic humans

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Inhibition of shivering increases core temperature afterdrop and attenuates rewarming in hypothermic humans. J. Appl. Physiol. 83(5): 1630–1634, 1997.—During severe hypothermia, shivering is absent. To simulate severe hypothermia, shivering in eight mildly hypothermic subjects was inhibited with meperidine (1.5 mg/kg). Subjects were cooled twice (meperidine and control trials) in 8°C water to a core temperature of 35.9 ± 0.5 (SD) °C, dried, and then placed in sleeping bags. Meperidine caused a 3.2-fold increase in core temperature afterdrop (1.1 ± 0.6 vs. 0.4 ± 0.2°C), a 4.3-fold increase in afterdrop duration (89.4 ± 31.4 vs. 20.9 ± 5.7 min), and a 37% decrease in rewarming rate (1.2 ± 0.5 vs. 1.9 ± 0.9°C/h). Meperidine inhibited overt shivering. Oxygen consumption, minute ventilation, and heart rate decreased after meperidine injection but subsequently returned toward preinjection values after 45 min postimmersion. This was likely due to the increased thermoregulatory drive with the greater afterdrop and the short half-life of meperidine. These results demonstrate the effectiveness of shivering heat production in attenuating the postcooling afterdrop of core temperature and potentiating core rewarming. The meperidine protocol may be valuable for comparing the efficacy of various hypothermia rewarming methods in the absence of shivering.

first aid; rate of rewarming; shivering thermogenesis; hypothermia treatment

IT IS GENERALLY AGREED that treatment of the hypothermic victim should minimize the postexposure afterdrop in core temperature (Tco) and promote a steady continuous rate of rewarming to a level at which thermal, cardiorespiratory, and metabolic homeostasis can be maintained. The appropriate method of treatment may depend on the level of hypothermia. In mild-to-moderate hypothermia, vigorous shivering produces considerable endogenous heat, which often masks potential benefits of various exogenous rewarming techniques (5, 13, 15, 16). One notable sign of severe hypothermia is the termination of shivering (12). The consequent decrease in endogenous heat production would likely result in a greater postcooling fall in Tco (afterdrop) and minimize any potential for spontaneous core rewarming. Such a condition would be unfavorable because the terminal event in accidental hypothermia is usually cold-induced ventricular fibrillation or cardiac arrest (2). Therefore, the magnitude of the effect of shivering suppression would be a valuable factor when consideration is given to treatment strategies for severe hypothermia.

In-depth study of severe hypothermia is difficult because experimental study of humans is confined to mild hypothermia (Tco > 33–35°C), whereas clinical reports are generally retrospective and involve highly variable circumstances. To evaluate the possible importance of shivering suppression, we have developed a human protocol that inhibits shivering, decreases metabolism, and produces cold body tissue, with appropriate periphery-to-core temperature gradients, within clinically safe Tco limits. The narcotic drug meperidine is commonly used to inhibit postoperative shivering (22). Because it has immediate onset when given intravenously and has a short duration of action (2–4 h) (20), this drug is attractive for experimental use to effectively abolish shivering during mild hypothermia.

To evaluate the possible importance of shivering suppression associated with severe hypothermia, we induced immersion hypothermia in human volunteers and compared physiological responses during two spontaneous rewarming protocols: 1) with shivering intact and 2) with shivering inhibited by meperidine. We hypothesized that the inhibition of shivering heat production would result in a greater postimmersion afterdrop in Tco with little or no subsequent increase in Tco.

METHODS

Subjects. With approval from our Faculty Human Ethics Committee, eight healthy subjects (2 women, 6 men) were studied after giving informed consent. The subjects were without allergy history or adverse reactions to or chronic use of narcotics. The eight subjects were 29.5 ± 5.7 (SD) yr old, had a mass of 78.9 ± 9.0 kg, were 178 ± 5.9 cm tall, had a sum of four skinfolds (biceps, triceps, suprailiac, and subscapularis) of 43.9 ± 12.0 mm, and had 16.9 ± 3.4% body fat (8).

Subjects were studied on two occasions at least 48 h apart. They were instructed to abstinence from alcohol and medications for a period of 24 h before each study. During cold-water immersion they received injections of either saline (control) or meperidine. They then exited the water and lay in an insulated sleeping bag for potential rewarming by means of endogenous heat production only.

Instrumentation. On each study day, subjects dressed in a swimsuit and were prepared in a room at an ambient temperature of ~22°C. Esophageal temperature (Tes) was measured by an esophageal thermocouple positioned at the level of the heart because this site provides the best noninvasive representation of core blood temperature (6, 19). Single-
channel electrocardiogram and heart rate were monitored continuously, and an intravenous line was introduced into a right arm or hand vein for drug and/or saline administration.

Thermal flux transducers (Concept Engineering, Old Saybrook, CT) were used to measure cutaneous heat flux and skin temperature (Tsk) at the following five sites: forehead, chest lateral of midline, abdomen lateral of midline, upper forearm, and mid thigh. Flux was defined as positive when heat traversed skin toward the environment (14). Body surface area (BSA) was calculated [BSA (m²) = weight (kg)·height(0.725)·0.007184], and the following regional percentages were assigned based on those of Layton et al. (21): head, 7%; chest, 19%; abdomen, 19%; arms, 20%; and legs, 35%. Flux values from each transducer (W/m²) were then converted into watts per region [flux at region (W) = transducer flux (W/m²)·BSA (m²)·regional percent·0.01].

Oxygen consumption (VO₂) was determined by an open-circuit method from measurements of expired minute ventilation (Ve) and inspired and mixed expired gas concentrations sampled from a 10-liter fluted mixing box. Ve was monitored by a pneumotachometer (model 47304A flow transducer, Hewlett-Packard) placed in the inspiratory circuit proximal to the mixing box. Mixed expired oxygen was sampled from the mixing box at 500 ml/min and analyzed by a Beckman OM-11 O₂ sensor (Beckman, Anaheim, CA) for O₂ fraction.

Analog data from the thermocouples, thermal flux transducers, gas analyzer, and pneumotachometer were acquired by using an electrically isolated Macintosh IIC computer. Data were scaled by using appropriate corrections and, where applicable, the calculated BSA. At 30-s intervals, the results were averaged for the preceding 30-s period, displayed graphically on the computer screen, and recorded in spreadsheet format on a hard disk. The process was controlled by a “virtual instrument” written by using LabVIEW II graphic signal-processing software (National Instruments, Austin, TX).

Protocol. Before immersion, subjects sat quietly for a period of 10 min, during which baseline data were collected. For both trials, they were then immersed (by using an electrically isolated hoist) to the sternal notch in a stirred water bath in which the water temperature was lowered from 20 to 8°C within 10 min by the addition of ice. They remained in the water until the final injection was made (see below). An attempt was made to adjust immersion times such that drug or placebo injections would be complete, and the subjects removed from the cold water, at a Tco of 36°C. This required between 35 and 70 min, depending on individual body composition and metabolic response to cooling. Greater core cooling was not attempted because this length of cold-water immersion was sufficient to produce significant tissue cooling, and further increases in thermal stimuli may necessitate higher doses of meperidine for complete suppression of shivering.

For comparative purposes, the immersion time and removal TX responses. During immersion, TEs decreased at a similar rate for both conditions (Fig. 1). TEs was significantly lower with meperidine from 10 min postimmersion to the end of the rewarming period (P < 0.01). The afterdrop with meperidine (1.1 ± 0.6°C) was three times greater than during control (0.4 ± 0.2°C; P < 0.005). Similarly, the afterdrop length was over four times longer during meperidine (89.4 ± 31.4 min) than during control (20.9 ± 5.7 min) trials (P < 0.0001). The rewarming rate during control (1.9 ± 0.9°C/h) was significantly higher than with meperidine (1.2 ± 0.5°C/h; P < 0.05).

Metabolic and cardiorespiratory responses. Before injections, shivering heat production increased throughout cooling (Fig. 1). In the control trials, VO₂ continued to increase, with maximum values coinciding with the nadir in TEs. Meperidine injection caused a rapid decrease in shivering, with VO₂ falling continually until 15 min postimmersion. VO₂ then rose gradually over the next 30 min, indicating diminished inhibition by meperidine of shivering heat production. This partial recovery of shivering was associated with termination of the relatively large afterdrop and subsequent slow rewarming rate.

Ve paralleled the VO₂ results for both treatments, rising steadily from 11.1 ± 2.3 l/min during baseline to 18.9 ± 6.4 l/min just before injections. In the control trials, Ve continued to increase to a maximum value of 26.4 ± 6.4 l/min 15 min postimmersion and subse-
quenty decreased to baseline values over the next 45 min. \( V_{\dot{E}} \) for meperidine trials was significantly lower than for control for the final 5 min of immersion and throughout the postimmersion period (\( P < 0.005 \)). After meperidine injections, \( V_{\dot{E}} \) steadily decreased to below baseline levels by 15 min postimmersion. \( V_{\dot{E}} \) then rose to 13.1 ± 2.0 l/min 45 min postimmersion and subsequently decreased toward baseline.

Heart rate was similar in the two conditions during baseline and cooling periods before the start of injections, with rates remaining near baseline values (Fig. 2). During control, heart rate then rose slightly until 10 min postimmersion followed by a decrease to subbaseline values. In the meperidine trial, heart rate decreased after meperidine injection until 10 min postimmersion and remained below baseline values for the remainder of the postimmersion period. During the meperidine trials an abrupt rise of short duration immediately postimmersion coincided with the transfer period and may reflect cardiac excitation above the meperidine-inhibited level due to voluntary motor activity and/or postural changes.

Heat transfer. Cutaneous heat flux increased similarly in control and meperidine trials, from 103 ± 15 W during baseline to 465 ± 129 W early in immersion with a subsequent decrease to 382 ± 91 W by the end of immersion. Postimmersion heat flux stabilized at a higher value during control trials (61 ± 20 W) than during meperidine trials (43 ± 12 W) (\( P < 0.05 \)). Net heat gain was similar in both conditions until injections (Fig. 3). Postimmersion net heat gain was consistently greater in the control trials by 87–158 W with the differences being significant for the first 15 min (\( P < 0.05 \)). During cooling the cumulative change in body heat content was similar in both conditions (Fig. 3). Postcooling body heat content was restored at a greater rate during control trials.

In both conditions, mean \( T_{sk} \) decreased from baseline values of 32.6 ± 0.6 to 21.7 ± 1.8°C throughout the immersion period. During postimmersion in the control trials, \( T_{sk} \) increased continually to a value of 30.5 ± 1.3°C after 30 min. In the meperidine trials, mean \( T_{sk} \) increased at a slower rate, to only 29.0 ± 1.6°C after 30 min postimmersion and finally reaching 31.8 ± 1.3°C after 80 min. Mean \( T_{sk} \) was significantly greater in control vs. meperidine trials from 15 min postimmersion until the end of the trials (\( P < 0.02 \)).

**DISCUSSION**

Meperidine effectively blocked shivering heat production for sufficient time to clearly demonstrate the effectiveness of shivering in minimizing the magnitude of postcold exposure afterdrop of \( T_{co} \). Inhibition of shivering in the meperidine trials resulted in a threefold increase in \( T_{co} \) afterdrop and more than a fourfold...
increase in length of the afterdrop period. Although Tco did increase late in the meperidine trials, the rewarming occurred at a very low rate and did not commence until 30 min after the slight disinhibition of shivering occurred.

Afterdrop values for the control condition (0.4°C) were within the range previously reported for shivering subjects (0.0–0.6°C) (3, 5, 10, 11, 13, 19). In the meperidine condition the afterdrop (1.1°C) was greater than previously reported in subjects who were not actively warmed (3, 5, 10, 11, 13, 19). Collis et al. (5) cooled nine subjects in 7.5°C water to Tco of 35°C and reported that three of the subjects did not shiver overtly during rewarming. The increase in tympanic temperature afterdrop in their spontaneously nonshivering subjects (0.80°C), compared with their shivering subjects (0.55°C), was qualitatively similar to our present results, although their nonshivering-to-shivering afterdrop ratio (1.5) was less than we report (3.2).

The rate of rewarming for the control shivering-intact condition (1.9°C/h) was within the range of rewarming rates previously reported for shivering subjects (0.6–4.9°C/h) (3, 5, 10, 11, 13, 19, 23, 26). The rate during nonshivering meperidine trials (1.2°C/h) was near the minimum values previously reported for human subjects (23, 26). Although Collis et al. (5) studied three apparently nonshivering subjects, they did not measure VO2 or report individual rewarming rates; therefore, a comparison of our nonshivering data with other nonshivering subjects is not possible.

The magnitude of Tco afterdrop depends on the following factors: conductive heat loss along tissue thermal gradients (18, 27), convective heat loss through changes in peripheral blood flow (4, 10), and local metabolic heat production in the periphery. First, it is unlikely that there was any intercondition difference in temperature gradients within the body because the cooling period was similar in both conditions. Regarding the second mechanism, distal tissue perfusion would have to increase in the meperidine trial to facilitate an increased afterdrop. The lower average Tsk and total heat flux during meperidine trials are consistent with an actual decrease in cutaneous blood flow. Also, peripheral muscular flow would be expected to decrease along with shivering in the meperidine trials. A decrease in both cutaneous and muscle blood flow would actually attenuate the afterdrop in the meperidine trials. It, therefore, appears that the increased afterdrop with meperidine is mainly due to decreased metabolic heat production. Major loss of shivering heat production significantly impairs buffering of heat loss from the core that occurs when shivering heat attenuates the thermal gradients for convective and conductive heat loss to colder peripheral tissues.

In several ways our results during shivering inhibition approximate the conditions of severe hypothermia. Throughout the rewarming period, meperidine reduced metabolism, ventilation, and heart rate. These responses are similar to those seen in severely hypothermic laboratory animals (28) and human patients (2). Although the tissue temperature gradients in the present study would not be as great as in a severely hypothermic patient, they were enough to evoke a greater afterdrop (1.1°C) than previously reported in spontaneously warming mildly hypothermic humans. In the severely hypothermic condition (i.e., Tco < 30°C), shivering would be completely suppressed (2), basal heat production would be only ~60% of normal (based on the Q10 principle), and there would be greater net heat loss than in the present study (27). These factors could potentiate a large afterdrop of a magnitude similar to those previously reported in nonshivering conditions. Cooled anesthetized dogs have been shown to have an afterdrop of up to 3°C (28), and severely hypothermic prisoners of war (Tco <30°C) had afterdrop values of 3–5°C (1). Such a decrease may be imminently life threatening if the temperature of the heart drops below thresholds for cardiac dysfunction (~28°C) or even to levels where spontaneous arrest may occur (<25°C) (2).
Although it would be preferable to experimentally study actual severely hypothermic subjects, ethical considerations contraindicate such a practice. Although the magnitude of cold stress and the responses to cooling are likely less in the present protocol than in an actual severe hypothermic condition, the metabolic and thermal responses are qualitatively similar. Therefore this shivering-inhibition protocol may be useful to compare the efficacy of various rewarming methods without the competing effect of shivering heat production (17). The slight disinhibition of shivering later in the meperidine trial was likely a result of enhanced central thermal drive during the exaggerated afterdrop and/or the diminished effect of meperidine as it was metabolized (i.e., the half-life of meperidine is 3 h) (20). The protocol could be improved by providing supplemental doses of meperidine during the rewarming period, inducing less hypothermia to decrease the central thermal drive during the exaggerated afterdrop, and/or attenuating rewarming. This shift could provide valuable information regarding treatment of nonshivering hypothermia. These studies might provide valuable information regarding treatment of nonshivering hypothermia. This study was supported by the Natural Science and Engineering Research Council of Canada; the Manitoba Health Research Council; Augustine Medical, Inc.; and the University of Manitoba Research Grants Committee.

In summary, the present protocol is the first to demonstrate that inhibition of shivering potentiates postcooling afterdrop and attenuates rewarming. This protocol provides an opportunity to compare strategies for treatment of nonshivering hypothermia. These studies might provide valuable information regarding treatment of life-threatening severe hypothermia at the rescue site to present the hypothermic victim in the best possible condition for subsequent hospital treatment. We thank Ohmeda, Inc., for the use of the pulse oximeter. This study was supported by the Natural Science and Engineering Research Council of Canada; the Manitoba Health Research Council; Augustine Medical, Inc.; and the University of Manitoba Research Grants Committee.

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