Metabolic benefits of surface counter warming during therapeutic temperature modulation*

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Objective: **To determine the impact of counter warming (CW) with an air circulating blanket on shivering and metabolic profile during therapeutic temperature modulation (TTM).**

Design: **A prospective observational study.**

Setting: **An 18-bed neurologic intensive care unit.**

Patients: **Fifty mechanically ventilated patients with brain injury undergoing TTM with automated surface and intravascular devices.**

Interventions: **Fifty indirect calorimetry (IDC) measurements with and without CW during TTM.**

Measurements and Main Results: **IDC was continuously performed for 10–15 minutes at baseline with CW (phase I), off CW (phase II), and again after the return of CW (phase III). Shivering severity during each phase was scored on a scale of 0−3 using the Bedside Shivering Assessment Scale (BSAS). Resting energy expenditure (REE), oxygen consumption, and carbon dioxide production were determined by IDC; 56% were women, with mean age 61 ± 15 years. At the time of IDC, 72% of patients had signs of shivering (BSAS >0). All measures of basal metabolism increased after removal of the air warming blanket (from phases I and II); REE increased by 27% and oxygen consumption by 29% (both $p < 0.002$). A one-point increase in baseline BSAS was noted in 55% (n = 23/42) of patients from phase I to phase II. In a multivariate analysis, sedative use ($p = 0.03$), baseline moderate to severe shivering ($p = 0.04$), and lower serum magnesium levels ($p = 0.01$) were associated with greater increases in REE between phase I and phase II of CW. Phase III of CW was associated with a reversal in the increases in all metabolic variables.**

Conclusions: **Surface CW provides beneficial control of shivering and improves the metabolic profile during TTM. (Crit Care Med 2009; 37:1893–1897)**

KEY WORDS: energy expenditure; hypothermia; normothermia; shivering; indirect calorimetry; brain injury; counter warming

With increasing use of advanced devices to control core body temperature, clinicians find it primarily difficult to achieving and maintaining goal temperature during shivering (1–3). This is an integrated thermoregulatory reflex triggered by a core body temperature that is lower than the hypothalamic set point, resulting in two simultaneous processes: involuntary, oscillatory muscular activity; and cutaneous vasoconstriction. Together, these responses generate heat in an effort to maintain a set core body temperature (4). Many of the pharmacologic agents that can counter shivering work to inhibit this response centrally; however, as a side effect, these can obscure the neurologic assessment (1).

Alternatively, the shivering–vasoconstrictive response can be combated by altering the cutaneous response to changes in body temperature. Mean skin temperatures contribute approximately 20% to the control of shivering with (5) or without (6) general anesthesia, and a reduction of skin temperature from 33°C to 30°C, despite a constant brain temperature, has been shown to initiate shivering (7). Forced-air warming systems increase skin temperature by 2°C to 3°C (8), and in the postoperative setting, they have been shown to be efficient in preventing postanaesthetic shivering (9) or rapidly inhibiting it when it occurs (10). The use of a forced air warmer in the recovery room can reduce the frequency (11, 12) and impact (12) of postanaesthetic shivering.

Based on the success of controlling shivering with counter warming (CW) in previous studies on temperature modulating devices (13, 14), we have utilized surface CW as the baseline antishivering measure in our patients undergoing therapeutic temperature modulation (TTM). However, the metabolic impact of surface CW while simultaneously cooling a patient remains unclear. Therefore, we designed a study to assess the impact of cutaneous warming on energy expenditure measurements in patients with brain injury undergoing TTM.

METHODS

Study Design. This was a prospective observational study of periodic shivering and indirect calorimetry (IDC) assessments in patients with brain injury, who underwent TTM for fever (15–17), elevated intracranial pressure (18), or cardiac arrest (19) as part of routine clinical care according to established protocols in our intensive care unit. Potential subjects were screened on morning rounds

*See also p. 2106.

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and recruited after verbal consent was provided by the patient or a family member. The study was approved by the Columbia University Institutional Review Board.

Indirect Calorimetry. Studies were performed once a day at the time of a shivering assessment using a Vmax Spectra (Sensormedic, Anaheim, CA) to measure inspired and expired concentrations of oxygen (O_2), CO_2, and minute ventilation. This open circuit system conducts continuous measurements of oxygen and CO_2 concentration in the inspired and expired air, allowing calculation of oxygen consumption (V_{O_2}, mL/min) and carbon dioxide production (V_{CO_2}, mL/min), time averaged during 60 seconds. From this information, the resting energy expenditure (REE) (kcal/d) is calculated using the Weir equation (20):

$$REE = (3.9 \times V_{O_2}) + 1.1 \times (V_{CO_2})$$

A certified technician (E.S.) conducted regular device calibration according to manufacturer guidelines to ensure accuracy of the oxygen and CO_2 sensory equipment. The baseline IDC measurements were based on a steady state, which was defined as a 20-minute interval during which average minute V_{O_2} and V_{CO_2} changed by <5% and <10%, respectively. Data were recorded every 60 seconds throughout the entire IDC session. IDC studies were not performed in patients who required fraction of inspired oxygen >50%, were known to be seizing, or had signs of early spasticity. The absence of seizure in obtunded or comatose patients was confirmed by continuous video electroencephalography at the time of IDC. Each of these conditions has been previously shown to alter the reliability of IDC measurements (21).

Counter Warming. Surface CW was achieved by covering the anterior surface of the patients with an air circulating blanket (BAIR Hugger, AZant Healthcare, Eden Prarie, MN) warmed to the maximal temperature setting (43°C). As part of routine care, all patients in our intensive care unit had surface CW in place during TTM. For purposes of this study, all patients had blankets in place for at least 30 minutes before IDC baseline measurements, as outlined earlier (phase I). The surface warming blanket was then removed, and continuous metabolic measurements were continued for another 10–15 minutes (phase II). The warming blanket was subsequently placed back onto the patient, and metabolic measurements were continued for another 10–15 minutes (phase III). During the study period, no changes were made to sedative medication usage.

Therapeutic Temperature Modulation. Target temperatures for fever control ranged between 36.5°C and 37.0°C, whereas the target temperature for hypothermia ranged between 33.0°C and 35.5°C. Fever control was defined as the application of a temperature regulating device to induce and maintain normothermia (37.0°C) in a patient who was febrile. Hypothermia was targeted at 33°C for all patients with cardiac arrest, and between 33.0°C and 35.5°C for all other patients based on the goal for intracranial pressure control and individual patient response to cooling.

Cooling was performed with either an intravascular (Celsius Control System, Innercool Therapies, San Diego, CA) or surface cooling (Arctic Sun Cooling System, Medivance, Louisville, CO) device. Decisions regarding the method and duration of cooling were left to the discretion of the attending neurointensivist. The administration of acetaminophen (650 mg Q4 hours) was continued in patients undergoing therapeutic normothermia. In both normothermia and hypothermia patients, measures to combat shivering included the standard administration of buspirone (30 mg orally Q8 hours) and skin CW with forced air warmed to the maximal temperature (43°C) setting (BAIR Hugger, AZant Healthcare) according to our intensive care unit protocol. Subsequent use of intravenous analgo-sedation to treat shivering with propofol, dexmedetomidine, meperidine, or fentanyl was decided on a case-by-case basis by the neurocritical care team. Administration and dosage of any sedative medication within 2 hours of IDC was recorded and included in analysis.

Bedside Shivering Assessment Scale. An assessment of shivering immediately before the initiation of IDC was performed and again when CW was discontinued. The Bedside Shivering Assessment Scale (BSAS) score has previously been reported to be a valid predictor of the metabolic demand of shivering during TTM (22). This four-point scale rates shivering as absent, mild, moderate, or severe.

Statistical Analysis. Baseline characteristics and measures of energy expenditure, hypermetabolic index, V_{CO_2}, and V_{O_2} were measured as either continuous variables with reported mean ± SD or as categorical variables with reported count and proportions (%) for each of the categories. Averages of the metabolic measurements during each of the phases of CW were compared using analysis of variance (ANOVA). A *post hoc* analysis utilizing a least significant difference was performed to assess any differences in metabolic measurements between phases of CW. Mean differences in metabolic variables between phases I and II among categorical and continuous baseline factors were assessed using a two-sided independent Student's *t* test and Pearson's correlation coefficient, respectively. Variables found to have a $p < 0.20$ were entered into a multivariable linear regression model to predict phase I to phase II changes in metabolic variables. Data were analyzed with commercially available statistical software (SPSS version 15.0, SPSS, Chicago, IL).

RESULTS

Baseline Characteristics. Between January and December 2006, 50 patients underwent 50 IDC tests. Clinical characteristics at the time of IDC testing are noted in Table 1. Each patient underwent only one assessment per day.

Patients diagnosed with subarachnoid hemorrhage (SAH) comprised the majority of subjects (n = 32/50, 64%). As compared to other patients, patients with SAH had no significant difference in V_{O_2} (305 ± 97 mL/min vs. 262 ± 72 mL/min, $p = 0.10$), V_{CO_2} (208 ± 58 mL/min vs. 190 ± 64 mL/min, $p = 0.3$), or REE (2021 ± 614 kcal/d vs. 1766 ± 453 kcal/d, $p = 0.13$). Patients with SAH had a higher incidence of shivering (BSAS ≥1 = 81% vs. 56%, $p = 0.05$). There was no significant difference in the age (60 ± 16 years vs. 63 ± 13 years, $p = 0.7$), gender (women: 59% vs. 50%, $p = 0.6$), body mass index (28 ± 4 kg/m^2 vs. 27 ± 4 kg/m^2, $p = 0.9$), body surface area (2.0 ± 0.2 m^2 vs. 1.8 ± 0.1 m^2, $p = 0.5$), or temperature goal (normothermia: 94% vs. 83%, $p = 0.3$) when comparing patients with SAH to the other patients in the study.

Impact of Surface CW on Shivering and Metabolic Measurements. Core body temperatures did not significantly change with removal of CW (Δ°C: 0.04 ± 0.06, $p = 0.9$) for all patients. Baseline shivering status

Table 1. Baseline characteristics at the time of indirect calorimetry testing; demographic characteristics of patients undergoing indirect calorimetry testing

Characteristic	n = 50
Age (yrs), mean ± SD	61 ± 15
Female (%)	28 (56)
Body mass index (kg/m^2), mean ± SD	27 ± 4
Body surface area (m^2), mean ± SD	1.9 ± 0.2
Diagnosis (%)	
Intracerebral hemorrhage	9 (18)
Subarachnoid hemorrhage	32 (64)
Cardiac arrest	3 (6)
Traumatic brain injury	3 (6)
Ischemic stroke	3 (6)
BSAS score (%)	
0	14 (28)
1	20 (40)
2	8 (16)
3	8 (16)
Temperature goal (%)	
Normothermia[a]	44 (88)
Hypothermia[b]	6 (12)
Cooling method (%)	
Surface[c]	45 (90)
Intravascular[d]	5 (10)

BSAS, Bedside Shivering Assessment Scale.
[a]Goal core body temperature of 36.5°C–37.0°C; [b]goal core body temperature of 33.0°C–35.5°C; [c]arctic sun temperature management system; [d]celsius control system.

Table 2. Impact of surface counter warming on metabolic measurements; average measurement of metabolic parameters during each phase of counter warming

Measurement	Counter Warming			p
	Phase I	Phase II	Phase III	
REE (kcal/d)	1936 ± 566	2466 ± 1028	2104 ± 837	<0.001
V_{O_2} (mL/min)	291 ± 10	376 ± 160	319 ± 131	<0.001
V_{CO_2} (mL/min)	201 ± 59	235 ± 93	211 ± 78	<0.001

REE, resting energy expenditure; V_{O_2}, oxygen consumption; V_{CO_2}, carbon dioxide production.

p represents result of ANOVA testing. *Post hoc* testing demonstrated significant differences between each phase of counter warming.

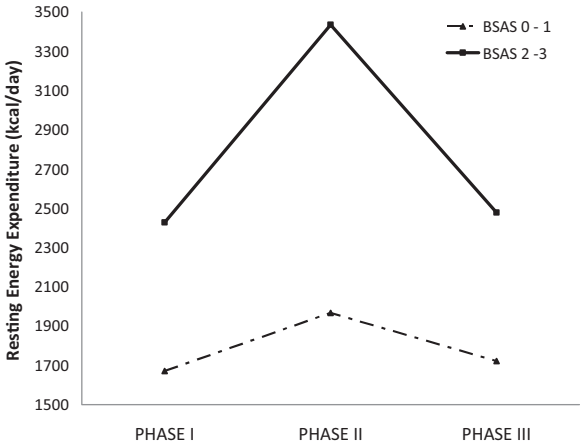

Figure 1. Changes in metabolic variables in phases I–III of counter warming depending on baseline shivering status. Comparison of the changes in metabolic variables from phase I to phase II of counter warming between no to mild shivering and moderate to severe shivering. ◆, no to mild shivering; ■, moderate to severe shivering; *BSAS*, Bedside Shivering Assessment Scale.

increased by one point in 55% (n = 23/42) of patients from phase I to phase II, and no patient had a decline in their BSAS score. A significant change in the average REE (ANOVA: $F = 60.9$, $p < 0.001$), V_{O_2} (ANOVA: $F = 63.1$, $p < 0.001$), and V_{CO_2} (ANOVA: $F = 31.2$, $p < 0.001$) was noted between phases I and III (Table 2). On *post hoc* analysis, there was a significant change in all metabolic variables between phases I and II ($p < 0.05$) and phases II and III ($p < 0.05$). However, there was no significant difference noted when assessing average difference in REE (ΔREE: −168 kcal/d, 95% CI: −48 to 194, $p = 0.1$), V_{O_2} (ΔV_{O_2}: −28 mL/min, 95% CI: −13 to −35, $p = 0.1$), V_{CO_2} (ΔV_{CO_2}: −10 mL/min, 95% CI: −6 to −16, $p = 0.4$) between phases I and III, respectively.

We did further subgroup analyses of characteristics that may have influenced the changes seen in shivering and metabolic measurements between phases of CW.

Therapeutic Temperature Modulation. The incidence of shivering at baseline was similar in normothermia as compared to hypothermia patients (75% vs. 50%, $p = 0.3$). We found no significant difference in the metabolic response to removal of CW when comparing normothermia with hypothermia patients (REE: 594 ± 351 kcal/d vs. 466 ± 305 kcal/d, $p = 0.4$; ΔV_{O_2}: 95 ± 79 mL/min vs. 75 ± 51, $p = 0.3$; ΔV_{CO_2}: 38 ± 14 vs. 30 ± 18, $p = 0.8$).

Nearly all patients underwent surface cooling (n = 45/50, 90%). Patients cooled by a surface device did not differ significantly in their metabolic response between phases I and II of CW as compared to patients cooled with an intravascular device (ΔREE: 504 ± 428 kcal/d vs. 557 ± 478 kcal/d, $p = 0.8$; ΔV_{O_2}: 81 ± 70 mL/min vs. 89 ± 72 mL/min, $p = 0.9$; ΔV_{CO_2}: 32 ± 9 mL/min vs. 36 ± 14 mL/min, $p = 0.9$).

Baseline Shivering Status. The majority of IDC tests were performed when there was at least mild shivering (BSAS ≥1 = 36/50 = 72%). At the time of testing, the presence of shivering (BSAS >0) was significantly associated with a lower body mass index (26.3 ± 4.6 kg/m^2 vs. 29.3 ± 1.9 kg/m^2, $p = 0.02$), body surface area (1.8 ± 0.2 m^2 vs. 2.0 ± 0.1 m^2, $p = 0.001$), and serum magnesium levels (1.8 ± 0.3 mg/dL vs. 2.4 ± 0.3 mg/dL, $p = 0.001$).

Patients with moderate to severe shivering (BSAS 2−3) had a significant increase in REE (ΔREE: 1022 ± 971 kcal/d vs. 299 ± 253 kcal/d, $p = 0.01$), oxygen consumption (ΔV_{O_2}: 160 ± 147 mL/min vs. 51 ± 38 mL/min, $p = 0.01$) and CO_2 production (ΔV_{CO_2}: 84 ± 97 mL/min vs. 10 ± 47 mL/min, $p = 0.01$) as compared to patients with no to mild shivering (BSAS 0–1) at baseline (Fig. 1).

Sedative Usage. Sedatives were administered to 40% (n = 20/50) of the patients within 2 hours of IDC measurement. Propofol infusion was the most commonly used sedative (n = 19, 38%) at a median dose of 86 mg·kg^{-1}·hr^{-1} (range: 23–250 mg·kg^{-1}·hr^{-1}). Fentanyl was used in 13% (n = 6/50) of patients at a median dose of 40 μg (25–50 μg), meperidine was used in 16% (n = 8/50) of patients at a median dose of 50 μg (range: 25–75 μg), and dexmedetomidine infusion was used in 6% (n = 3/50) of patients at a median dose of 0.4 μg·kg^{-1}·min^{-1} (range: 0.2–0.7 μg·kg^{-1}·min^{-1}). There was no significant relationship between the BSAS score and propofol dose (ANOVA $F = 0.5$, $p = 0.7$), meperidine dose (ANOVA $F = 1.1$, $p = 0.4$), dexmedetomidine dose (ANOVA $F = 0.2$, $p = 0.9$), and fentanyl dose (ANOVA $F = 1.1$, $p = 0.4$). However, the proportion of patients with moderate to severe shivering receiving sedatives was significantly higher as compared to those patients with no to mild shivering (88% vs. 18%, $p < 0.01$).

Patients receiving any sedation within 2 hours of the study period had a significant increase in all metabolic variables between phase I and phase II of CW (ΔREE: 847 ± 859 kcal/d vs. 229 ± 111 kcal/d, $p = 0.002$; ΔV_{O_2}: 134 ± 130 mL/min vs. 40 ± 16 mL/min, $p = 0.002$; ΔV_{CO_2}: 65 ± 92 mL/min vs. 4 ± 37 mL/min, $p = 0.006$).

Serum Magnesium Level. A lower baseline serum magnesium level (REE: $R = -0.59$, $p < 0.001$; V_{O_2}: $R = -0.56$, $p < 0.001$; V_{CO_2}: $R = -0.57$, $p < 0.001$) correlated with a significant increase in the metabolic measurements between phase I and phase II of CW.

Multivariable Models of Factors Influencing Metabolic Rate Between Phase I and Phase II of CW. In a multivariable linear regression model adjusting for the diagnosis of SAH, the increase in REE (ΔREE) and oxygen consumption (ΔV_{O_2})

Table 3. Factors associated with the changes in metabolic parameters between phase I and phase II of counter warming

	ΔV_{O_2}[a]	ΔV_{CO_2}[b]	ΔREE
BSAS 2–3[c]	0.28[d]	0.17	0.26
p	0.04	0.2	0.04
Sedative use	0.27	0.21	0.26
p	0.03	0.1	0.03
Magnesium	−0.35	−0.37	−0.37
p	0.01	0.01	0.01

REE, resting energy expenditure; BSAS, Bedside Shivering Assessment Scale; V_{O_2}, oxygen consumption; V_{CO_2}, carbon dioxide production.

[a]Oxygen consumption; [b]carbon dioxide production; [c]bedside Shivering Assessment Scale Scores that represent moderate to severe shivering; [d]beta coefficient from the linear regression model. Multivariate linear regression models of factors that predict the change in metabolic parameters between phase I and phase II of counter warming. Models consist of patients diagnosed with subarachnoid hemorrhage, use of sedatives, and baseline serum magnesium levels.

measurements between phase I and phase II of CW were associated with patients who had lower serum magnesium levels, moderate to severe shivering (BSAS 2–3), and higher sedative use (Table 3). The diagnosis of SAH was not found to be significantly associated with any of the metabolic measurements in these multivariable models.

DISCUSSION

We found that the use of a warming blanket counters the metabolic impact of shivering during TTM. Surface warming works by countering the feedback loop from the skin temperature to the hypothalamic thermoregulation centers. Although previous surface warming studies used regional hand and face warming and did not find a significant benefit (23), we found that by covering the entire anterior surface, sparing the neck and face, surface CW is beneficial. This greater proportion of surface warming likely had a greater effect on the mean skin temperature and impact on the feedback to the hypothalamic thermoregulatory centers. Cheng et al (24) have shown that a linear relationship exists between core temperature and the average skin temperature for the appearance of shivering in the nonanesthetized patient. The threshold temperature for shivering is equal to the sum of 20% of the mean skin temperature and 80% of the core temperature. Therefore, to inhibit shivering, the average skin temperature must be raised by at least 4°C to be as efficient as a 1°C increase in core temperature (24). Although the surface warming device was turned to the maximal temperature setting of 43°C, we did not assess shivering thresholds or directly measure the skin temperatures in our patients.

Each patient had a demonstrable metabolic benefit of surface CW, even when there was no or only mild shivering present at baseline. This reduces the concern of any counter effect of surface warming while inducing normothermia or hypothermia. The metabolic impact of CW did depend on the baseline shivering status of patients with no to mild shivering (BSAS 0–1, respectively) having a diminished response to removal of surface CW as compared to patients with moderate to severe shivering (BSAS 2–3, respectively) (Fig. 1). This means that among patients with moderate to severe shivering, the combination of surface CW and buspirone have a significant but incomplete effect in ameliorating the metabolic implications of shivering, indicating the importance of finding additional methods to control shivering.

An alternative, nonsedating regimen would be to continue targeting the peripheral mechanisms of cutaneous vasoconstriction or skeletal muscular activity. Infusions of dantrolene have been shown to reduce both the severity and threshold for shivering (25); however, this may lead to prolonged muscular weakness and increased number of ventilator days, and therefore, limit its usefulness.

Additional targeting of the cutaneous vasoconstrictive response, however, may still be possible with the intravenous administration of magnesium. As seen in this study and previous assessments of shivering (1), hypomagnesemia is a risk factor for not only baseline shivering but also response to surface CW. Magnesium at high doses reduces the shivering response or increases the rate of achieving mild hypothermia in healthy volunteers (26) and postoperative patients (27–29). The mechanism is related to its peripheral vasodilatory properties, which exert negative feedback control on the thermoregulation centers located in the preoptic nucleus of the hypothalamus (28). Unlike pharmacologic interventions used to suppress shivering, magnesium infusion is not associated with a sedative effect and has potential neuroprotective (30) properties. Therefore, the administration of high doses of magnesium sulfate to prevent shivering in this patient population may be a well-suited adjunctive therapy and should be further studied.

This study is limited in its generalizability by the fact that the majority of patients underwent normothermia with a surface cooling device; however, there is no reason to believe that the metabolic benefit of surface CW would not translate readily to other depths of cooling. This is likely due to the fact that the incidence of shivering is dependent on the shivering threshold, with a lower incidence occurring at temperatures <35.5°C. However, the intensity of shivering, which is what our energy expenditure measurements and the BSAS measured, is more dependent on activation of muscles than core body temperature (31). Although we did not find a significant difference in the impact of CW with an intravascular device, the number of patients cooled with this method was low (n = 5). Patients cooled with intravascular devices will have more exposed body surface area and therefore may benefit more from CW. This study was designed to address a physiologic end point, and so the effect of reducing shivering with CW as it relates to clinical outcome was not measured. Shivering and its counter measures may impact on the outcome (1) in patients undergoing TTM and should be incorporated into any prospective study of TTM.

CONCLUSION

Whole body surface CW during TTM represents a simple, nonsedating method to combat the metabolic impact of shivering. This technique, however, does not provide adequate shiver control for all patients. Future studies should focus on minimally sedating antishivering regimens that can provide additional benefit when surface CW fails.

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