Metabolic Impact of Shivering During Therapeutic Temperature Modulation

The Bedside Shivering Assessment Scale

Neeraj Badjatia, MD, MSc; Evangelia Strongilis, RD; Errol Gordon, MD; Mary Prescutti, RN; Luis Fernandez, MD; Andres Fernandez, MD; Manuel Buitrago, MD, PhD; J. Michael Schmidt, PhD; Noeleen D. Ostapkovich, MSc; Stephan A. Mayer, MD, FCCM

Background and Purpose—Therapeutic temperature modulation is widely used in neurocritical care but commonly causes shivering, which can hamper the cooling process and result in increases in systemic metabolism. We sought to validate a grading scale to assist in the monitoring and control of shivering.

Methods—A simple 4-point Bedside Shivering Assessment Scale was validated against continuous assessments of resting energy expenditure, oxygen consumption, and carbon dioxide production as measured by indirect calorimetry. Therapeutic temperature modulation for fever control or the induction of hypothermia was achieved with the use of a surface or endovascular device. Expected energy expenditure was calculated using the Harris–Benedict equation. A hypermetabolic index was calculated from the ratio of resting of energy expenditure to energy expenditure.

Results—Fifty consecutive cerebrovascular patients underwent indirect calorimetry between January 2006 and June 2007. Fifty-six percent were women, and mean age 63±16 years. The majority underwent fever control (n=40 [80%]) with a surface cooling device (n=44 [87%]) and had signs of shivering (Bedside Shivering Assessment Scale 0, 64% [n=34 of 50]). Low serum magnesium was independently associated with the presence of shivering (Bedside Shivering Assessment Scale 0; OR, 6.8; 95% CI, 1.7 to 28.0; P=0.01). The Bedside Shivering Assessment Scale was independently associated with the hypermetabolic index (W=16.3, P<0.001), oxygen consumption (W=26.3, P<0.001), resting energy expenditure (W=27.2, P<0.001), and carbon dioxide production (W=18.2, P<0.001) with a high level of interobserver reliability (κw=0.84, 95% CI, 0.81 to 0.86).

Conclusion—The Bedside Shivering Assessment Scale is a simple and reliable tool for evaluating the metabolic stress of shivering. (Stroke. 2008;39:3242-3247.)

Key Words: hypothermia ■ intracerebral hemorrhage ■ ischemic stroke ■ normothermia ■ shivering ■ subarachnoid hemorrhage

Fever has been linked with poor outcome after ischemic stroke,1 subarachnoid hemorrhage,2,3 and intracerebral hemorrhage.4 Induced hypothermia is useful for control of elevated intracranial pressure5 and has been shown to improve survival and functional outcome after cardiac arrest.6,7 Maintenance of normothermia after ischemic and hemorrhagic stroke and therapeutic hypothermia for cardiac arrest are part of the American Heart Association’s clinical guidelines. Accordingly, many neurocritical care centers are increasingly using protocols for therapeutic temperature modulation in the setting of acute cerebrovascular injury.

New technology has made the induction and maintenance of therapeutic normothermia and hypothermia feasible with both surface and intravascular devices.8–10 An important adverse effect of therapeutic temperature modulation is shivering.10,11 Shivering results in sharp increases in resting energy expenditure (REE) and in the systemic rate of oxygen consumption (VO₂). These findings have previously been validated with the use of indirect calorimetry (IDC),12,13 the standard for the measurement of energy expenditure in the clinical setting.14 Left uncontrolled, shivering can defeat the cooling process and eliminate the potential benefits of therapeutic normothermia15 and in extreme cases may be more detrimental than fever itself.16

During the course of providing clinical care, a simple scale that clinicians can use to assess the severity of shivering is currently unavailable. The ability to differentiate the graded metabolic response to shivering would provide valuable
clinical information, particularly as an end point for antishivering interventions. In this study, we sought to develop and validate a simple grading scale—the Bedside Shivering Assessment Scale (BSAS)—by assessing its correlation with systemic metabolic stress quantified by IDC.

Methods

Study Design
This was a prospective observational study of periodic shivering and IDC assessments in brain-injured patients who underwent therapeutic temperature modulation for fever, elevated intracranial pressure, or cardiac arrest as part of routine clinical care according to established protocols in our intensive care unit. Potential subjects were screened on morning rounds 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 daily at the time of a shivering assessment using a Vmax Spectra device (SensorMedics, Anaheim, Calif) to measure inspired and expired concentrations of oxygen (O\textsubscript{2}), carbon dioxide (CO\textsubscript{2}), and minute ventilation. This open circuit system conducts continuous measurements of oxygen and carbon dioxide concentration in the inspired and expired air, allowing calculation of oxygen consumption (VO\textsubscript{2}, mL/min) and carbon dioxide production (CO\textsubscript{2}, mL/min), with time averaged over 60 seconds. From this information, the REE (kcal/d) is calculated using the Weir equation:\textsuperscript{17}

\[
REE = (3.9 \times VO_2) + 1.1 \times (VCO_2)
\]

in which VCO\textsubscript{2} = carbon dioxide production.

The hypermetabolic index (HMI) for energy expenditure was derived by dividing the time-averaged measured value of REE (kcal/d) by expected energy expenditure (kcal/d). Expected energy expenditure values were derived from the Harris–Benedict equation,\textsuperscript{18} which were multiplied by 1.2 to 1.3 to adjust for patient acuity.

A certified technician (E.S.) conducted regular device calibration according to manufacturer guidelines to ensure accuracy of the oxygen and carbon dioxide sensory equipment. IDC studies were completed when a steady state was achieved, which was defined as a 20-minute interval during which average minute oxygen consumption (VO\textsubscript{2}) and carbon dioxide production changed by <5% and <10%, respectively. Data were recorded every 60 seconds during steady-state conditions. 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 have been previously been shown to alter the reliability of IDC measurements.\textsuperscript{18}

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 depending on the specific condition being treated. Cooling was performed with either an intravascular (Celsius Control System: Innercool Therapies, Inc, San Diego, Calif) or surface cooling (Arctic Sun Cooling System: Medivance Inc, Louisville, Colo) device. Decisions regarding the method and duration of cooling were left to the discretion of the attending neurointensivist. Measures to combat shivering included the standard administration of acetaminophen (650 mg every 4 hours), buspirone (30 mg orally every 8 hours), and skin counterwarming with forced air warmed to 43°C (BAIR Hugger; Arizant Healthcare, Eden Prairie, Minn) 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 indirect calorimetry was recorded and included in the analysis.

Bedside Shivering Assessment Scale
Several versions of a shivering scale were pilot tested by the neurointensive care unit physicians and nurses before this study; revisions were made to optimize simplicity and ease of use and to facilitate interobserver reliability. The final version deemed appropriate for study was a 4-point scale, which rates shivering as absent, or mild, moderate, or severe (Table 1). To accurately assess the BSAS score, all raters were asked to observe the patient for a period of 2 minutes, during which time they visually inspected and palpated the neck, thorax, arms, and legs. An assessment of shivering immediately before the initiation of indirect calorimetry was performed simultaneously by 2 physicians and 2 nurses. Raters were blinded to each other’s assessments as well as to the IDC measurements. At the end of each encounter, the BSAS blinding was broken to establish a consensus score for validation against the calorimetry findings. Disagreements were adjudicated by accepting the score of the majority. In event of a tie, each of the raters was asked to reassess the patient until a consensus could be reached.

Statistical Analysis
Baseline characteristics and measures of energy expenditure, HMI, carbon dioxide production, and oxygen consumption were compared between BSAS levels as well as with baseline characteristics either a Pearson’s correlation or 2-sided independent t test. Post hoc tests were used to determine any differences in REE, O\textsubscript{2} consumption, CO\textsubscript{2} production, or HMI between separate levels of BSAS. Laboratory values measured within 6 hours before IDC measurements were recorded in all patients. These data were represented as continuous data and compared using analysis of variance between various shivering states as determined by the BSAS. We tested interrater reliability by calculating weighted (K\textsubscript{w}) kappa scores, which numerically express the degree of agreement on an ordinal scale between 2 observers beyond chance.\textsuperscript{20} The calculation of kappa yields a value between 0 and 1; agreement is poor if K < 0.21, fair if K = 0.21 to 0.40, moderate if K = 0.41 to 0.60, good if K = 0.61 to 0.80, and excellent if K > 0.80.\textsuperscript{20}

Clinical variables found to have a probability value ≤0.2 were entered into a generalized linear model along with the BSAS score to ascertain the factors that independently predicted REE, HMI, O\textsubscript{2} consumption, and CO\textsubscript{2} production. Each of the metabolic parameters was entered into an ordinal logistic regression model to validate each level of the BSAS score. Data were analyzed with commercially available statistical software (SPSS version 15.0; SPSS, Chicago, Ill). For all analyses, P < 0.05 was considered significant.

Results

Baseline Characteristics
Fifty consecutive patients undergoing therapeutic normothermia or therapeutic hypothermia met study criteria between January 2006 and June 2007 (Table 2). Patients diagnosed with subarachnoid hemorrhage comprised the majority of

<table>
<thead>
<tr>
<th>Table 1. The Bedside Shivering Assessment Scale</th>
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<tr>
<td>Score</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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subjects (n=34 [68%]); there were no differences in baseline demographic and clinical characteristics between patients with subarachnoid hemorrhage and those without subarachnoid hemorrhage (data not shown).

### Indirect Calorimetry Assessments

Differences in systemic metabolism were not found between patients cooled to normothermia or hypothermia. However, REE, O₂ consumption, and CO₂ production were all higher in patients with a greater body mass index, body surface area, younger age, and male sex (Table 3). These measures of metabolism were also significantly increased in patients treated with intravenous sedatives to control shivering (Table 3). Propofol was the most commonly used sedative (n=18 [36%]) at a median dose 140.5 mg/kg/h (range, 30 to 450 mg/kg/h); there was no relationship between propofol dose and REE (r=0.1, P=0.7) or HMI (r=0.24, P=0.25). Fentanyl was used in 7 (14%) patients at a median dose of 40 μg (range, 25 to 50 μg), meperidine was used in 7 (14%) patients at a median dose of 50 μg (range, 25 to 75 μg), and dexmedetomidine was used in 4 (8%) patients at a median dose of 0.4 μg/kg/min (range, 0.2 to 0.7 μg/kg/min).

In multivariate models adjusting for body mass index, body surface area, age, sedative use, and male sex, sedative use was significantly associated with a higher HMI (β=0.8, P=0.02), REE (β=0.7, P=0.03), and O₂ consumption (β=0.7, P=0.03). Male sex was significantly associated with higher CO₂ production (β=0.5, P=0.05).

### Bedside Shivering Assessment Scale

The scale demonstrated a high level of interrater reliability (κ=0.84; 95% CI, 0.81 to 0.86). There were 5 instances (n=5 of 50 [10%]) in which there were ties that needed further testing. There was perfect agreement in 43 (86%) instances. Overall, during 32 of the 50 (64%) assessments, the BSAS documented clinical signs of shivering (BSAS >0). The breakdown of the 50 consensus shivering assessments was as follows: BSAS 0, 18 (36%); BSAS 1, 14 (28%); BSAS 2, 10 (20%), and BSAS 3, 8 (16%). The BSAS was significantly associated with all metabolic parameters evaluated using indirect calorimetry (Table 4). Post hoc analyses revealed that each level of the BSAS score was significantly different from the other on each of the metabolic parameters (P<0.05). The BSAS score was most strongly associated with the hypermetabolic index (Figure).

As noted in Table 4, the proportion of patients who received any sedation was highest with BSAS scores of 2 or 3. There was no difference in the mean dose of propofol administered (analysis of variance: F=1.3, P=0.3) among all
BSAS levels. To exclude the possibility that sedative use or temperature goal may have influenced the BSAS–energy expenditure relationship, we performed ordinal regression models adjusting for any sedative use and temperature goal and found increasing BSAS scores from 0 to 3 were independently associated with the hypermetabolic index (W=16.3, P<0.001), O2 consumption (W=26.3, P<0.001), REE (W=27.2, P<0.001), and CO2 production (W=18.2, P<0.001). Additionally, after adjusting for age, temperature goal, white blood cell count, and sedative use, low magnesium levels (OR, 6.8; 95% CI, 1.7 to 28.0; P=0.01) were associated with the presence of any shivering (BSAS >0).

A secondary analysis demonstrated that the metabolic reduction of therapeutic hypothermia as compared with normothermia was only seen in patients who had no to mild shivering as demonstrated by the average REE (1339±471 versus 1698±427 kcal/d, P<0.001), O2 consumption (187±72 versus 250±63 mL/min, P=0.005), CO2 production (162±47 versus 193±56 mL/min, P=0.05), and HMI (1.02±0.17 versus 1.15±0.11, P=0.005).

**Discussion**

Advanced temperature modulation techniques now allow for the elimination of fever as well as controlled hypothermia. However, as demonstrated in this study, shivering is frequently encountered (64%), and the severity of shivering as measured by the BSAS is strongly associated with graded increases in systemic metabolism. The application of therapeutic normothermia or hypothermia has not been shown to improve outcome after cerebrovascular injury, and the metabolic consequences of shivering may prove to be a limiting step in demonstrating the benefits of therapeutic temperature modulation. A scale that can simply and reliably detect and quantify shivering can be used as an end point for antisivering interventions and may play an important role in minimizing the day-to-day complications of cerebrovascular patients undergoing therapeutic temperature modulation in the intensive care unit.

Previous reports have considered shivering to be a binary event;8–10 however, the metabolic impact of shivering is proportional to its intensity and the affected muscle mass and can range in healthy individuals from 2- to 3-fold above expected energy expenditure.21 By clinically assessing muscular involvement in the trunk and limbs, the BSAS provides an accurate representation of the metabolic impact of shivering. The high interrater reliability of the BSAS means that assessments using this scale are reproducible as caregivers change during the course of care.

### Table 4. Characteristics of Shivering as Determined by the BSAS

<table>
<thead>
<tr>
<th>BSAS</th>
<th>0 (n=18)</th>
<th>1 (n=14)</th>
<th>2 (n=10)</th>
<th>3 (n=8)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, years, mean±SD</td>
<td>62±16</td>
<td>55±18</td>
<td>65±16</td>
<td>60±13</td>
<td>0.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25±4</td>
<td>24±6</td>
<td>26±3</td>
<td>27±2</td>
<td>0.4</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.8±0.3</td>
<td>1.8±0.3</td>
<td>1.8±0.2</td>
<td>1.9±0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>18 (72)</td>
<td>19 (80)</td>
<td>10 (63)</td>
<td>6 (60)</td>
<td>0.5</td>
</tr>
<tr>
<td>Therapeutic normothermia, n (%)</td>
<td>19 (84)</td>
<td>19 (79)</td>
<td>14 (88)</td>
<td>8 (80)</td>
<td>0.5</td>
</tr>
<tr>
<td>Surface cooling, n (%)</td>
<td>20 (80)</td>
<td>23 (96)</td>
<td>14 (88)</td>
<td>8 (80)</td>
<td>0.2</td>
</tr>
<tr>
<td>Sedative use, n (%)</td>
<td>12 (48)</td>
<td>8 (33)</td>
<td>10 (63)</td>
<td>10 (100)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
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<tr>
<td>Magnesium, mg/dL</td>
<td>2.4±0.5</td>
<td>2.2±0.5</td>
<td>1.8±0.0</td>
<td>1.7±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>151±9</td>
<td>154±10</td>
<td>149±12</td>
<td>148±11</td>
<td>0.6</td>
</tr>
<tr>
<td>White blood cell count, 10⁶/L</td>
<td>12.2±4.5</td>
<td>12.7±4.5</td>
<td>14.9±4.3</td>
<td>16.3±3.9</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>IDC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HMI</td>
<td>1.0±0.1</td>
<td>1.2±0.1</td>
<td>1.6±0.2</td>
<td>2.4±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REE, kcal/d</td>
<td>1390±383</td>
<td>1730±481</td>
<td>2303±688</td>
<td>3686±960</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O2 consumption, mL/min</td>
<td>198±62</td>
<td>251±74</td>
<td>337±119</td>
<td>568±152</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO2 production, mL/min</td>
<td>165±36</td>
<td>200±61</td>
<td>233±55</td>
<td>325±93</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure.** Relationship between the BSAS and the HMI.
The use of sedatives was found to be associated with both higher energy expenditure and with higher BSAS scores. This most likely reflects the fact that sedation was used to control shivering when it was present with higher doses used when it was more severe. Despite this, in a multivariate model adjusting for sedative use and temperature goal, the BSAS remained an accurate stepwise predictor of all measures of energy expenditure. Despite management protocol directed at maintaining serum magnesium levels $>2.0$ mg/dL, some patients had levels below this target on the day of IDC testing. Similar to a previous study, lower serum magnesium levels were associated with more severe shivering. The administration of magnesium induces muscle relaxation, resulting in a reduction in the intensity of shivering, and its nonsedating properties make the administration of magnesium a potentially useful adjunctive antishivering therapy.

The ability to accurately identify the intensity of shivering at the bedside has distinct advantages. A critical mechanism by which therapeutic temperature modulation confers neuroprotection is by reducing the cerebral metabolic rate by up to 15% for every 1°C reduction in core body temperature. However, these reductions in cerebral metabolism can be offset when shivering is uncontrolled. The BSAS allows clinicians to identify and quantify moderate or severe levels of shivering (scores of 2 or 3, respectively) that are associated with clinically important increases in systemic metabolism. The clinical consequences of shivering can include increased tissue ischemia, which has been associated with increased morbidity in postoperative patients who have undergone cardiac surgery. We have shown that shivering during therapeutic normothermia is associated with lower Glasgow Coma Scale scores in neurocritical care patients, which most likely reflects the sedation required to adequately treat shivering. The ability to titrate antishivering therapy with short-acting opioids or other sedative agents to a BSAS score of 1 might provide allow clinicians to eliminate harmful levels shivering without oversedating.

There are several limitations of this study. This scale was tested in a heterogeneous population with a variety of target core body temperatures. However, at each individual BSAS score, the metabolic response was accurately predicted despite whether the patient was cooled to normothermia or hypothermia. The consistent association between BSAS scores and changes in systemic metabolism across different diagnostic groups and indications for cooling enhances the practical usefulness of this scale.

Our largest subgroup of patients was subarachnoid hemorrhage. This population as well may be metabolically heterogeneous due to factors such as raised intracranial pressure or vasospasm, which may have influenced our findings. However, our analysis found no association between demographic or measured clinical and radiological variables and energy expenditure. Nonetheless, larger studies of the BSAS both within and across types of neurovascular injury will be needed to fully understand whether the BSAS score is influenced by such factors.

The number of patients who were a BSAS 3 was less than other groups, which was likely due to our institutional practice of attempting to aggressively treat severe shivering with an escalating pharmacological regimen. Although it is possible that study of additional BSAS 3 patients might significantly alter our findings, we feel that this is unlikely. The BSAS and metabolic parameters were not tracked continuously over several days nor were clinical outcome parameters measured; therefore, direct conclusions regarding the ability to accurately track the long-term metabolic impact of shivering and outcome cannot be made. Additionally, we did not track the metabolic and BSAS response to antishivering measures; therefore, we only speculate on the potential usefulness of the BSAS to measure dynamic changes in shivering and systemic metabolism.

Nonetheless, the BSAS is a simple, reliable tool that can be used to measure the metabolic impact of shivering. Future studies will focus on the ability of the BSAS to track the metabolic impact over a longer duration and in response to counter shivering measures.

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