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BRIEF REPORT

Juergen Bardutzky
Dimitrios Georgiadis
Rainer Kollmar
Stefan Schwab

Energy expenditure in ischemic stroke patients treated with moderate hypothermia

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J. Bardutzky (✉) · D. Georgiadis
R. Kollmar · S. Schwab
Department of Neurology,
University of Heidelberg,
Im Neuenheimer Feld 400,
69120 Heidelberg, Germany
e-mail:
juergen_bardutzky@med.uni-heidelberg.de
Tel.: +6221-5637842
Fax: +6221-564671

Abstract *Objective:* To determine total energy expenditure (TEE) in patients with acute ischemic stroke in the territory of the middle cerebral artery (MCA), treated with moderate hypothermia (33°C). *Design and setting:* Prospective study in a neurological ICU. *Patients:* Ten consecutive patients with severe MCA infarction undergoing moderate hypothermia. *Measurements and results:* Indirect calorimetry was performed continuously over the first 6 days after admission. Mean daily TEE decreased significantly from 1549 before initiation of hypothermia to 1099, 1129, and 1157 on the first, second, and third days of hypothermia, respectively and returned to baseline values after hypothermia was terminated. The ratio of TEE to predicted basal energy expenditure declined from 1.01 before induction of hypothermia to an average of 0.74 during steady state of hypothermia and increased to 1.16 after rewarming. *Conclusions:* We found a significant fall in TEE in sedated, curarized, and ventilated ischemic stroke patients during moderate hypothermia. Indirect calorimetry appears to be a useful tool for measuring energy expenditure in these patients, as predicted basal energy expenditure overestimates the caloric requirements during hypothermia.

Keywords Stroke · Hypothermia · Energy expenditure · Indirect calorimetry

Introduction

Moderate (33°C) hypothermia (MH) has been shown to be a potent treatment option in reducing intracranial hypertension in patients with large hemispheric infarction [1]. While the underlying pathophysiological mechanism is not yet fully understood, a reduction in excitatory amino acids [2], stabilization of the blood-brain barrier and cell membranes [3], and a decrease in metabolic activity have been postulated [4]. No study has yet examined the actual reduction in metabolic activity or in caloric demands in stroke patients treated with MH. This issue is crucial, however, as both under- and overfeeding are associated with various side effects in an intensive care setting [5]. This study examined the course of total energy expenditure (TEE) before, during, and after hypothermia in patients with severe middle cerebral artery (MCA) infarction using continuous indirect calorimetry (IC).

Patients and methods

Ten consecutive patients (six women, four men; average age 61 years, range 43–71) were treated with MH according to our institutional protocol [6]. The study protocol was approved by the local ethics committee standards. Cardiovascular risk factors were arterial hypertension (n=5), diabetes mellitus (n=4), and ischemic heart disease (n=3). Cardiac rhythm was sinus in six and atrial fibrillation in four cases. Six patients had suffered a complete MCA territory stroke, one of whom had additional anterior cerebral infarction and four MCA infarction involving at least two-thirds of the MCA territory. Induction and maintenance of hypothermia was performed with an endovascular cooling device, as described elsewhere [6]. Latency between onset of symptoms and initiation of hypothermia was 22.4 h (range 12–48) and average duration of hypothermia was 73.6 h (range 68-80). The time needed to reach

the target temperature of 33°C varied between 2.5 and 4.5 h. The maximal and minimal temperature values observed during hypothermia were 33.3°C and 32.7°C, respectively. Duration of rewarming ranged between 24 and 32 h.

All patients were sedated with a standard regimen of fentanyl (range 0.2–0.3 mg/h) and midazolam (range 10–14 mg/h), while atracurium (range 30–40 mg/h) was used for neuromuscular blockade; this regimen was continued until rewarming at 36°C was achieved. All patients were on volume-controlled ventilation, and the ventilator was adjusted to obtain a PaO_2 level higher than 95 mmHg and $PaCO_2$ of 35–40 mmHg; hyperventilation was not a part of our treatment regimen.

All patients received total parenteral nutrition (20% protein, 40% fat, 40% carbohydrates) due to the severely reduced ability to tolerate gastric feeding in deeply sedated, curarized hypothermic patients. A daily target caloric supply of 25 kcal/kg was reached within at least 4 days in each patient. With regard to the benefits of early enteral nutrition [7], additional small amounts of enteral feeding (range 100–400 ml/day; 1 kcal/ml) were administered daily via nasogastric tube beginning within 24–32 h after admission. Serum albumin concentration, a commonly used marker for patients' nutritional status, was determined on admission and after hypothermia (day 5).

IC is based on the principle that energy expenditure can be determined by measuring oxygen consumption and carbon dioxide production in inspired and expired gases. Oxygen consumption and carbon dioxide production were measured continuously from day 1 to day 6 after admission at 5-min intervals and the calculated energy expenditure values and respiratory quotient were recorded to obtain the average of a 24-h period (M-COVX, Datex Ohmeda, Finland). The basal energy expenditure (BEE; measured in kilocalories per day) was determined using the Harris-Benedict equation:

– Men: 66.5+13.75 W+5.003 H–6.775 A
– Women: 655.1+9.563 W+1.85 H–4.676 A

where W is weight (in kilograms), H is height (in centimeters), and A is age (in years).

The Lilliefors test was used to test normality of data distribution. Nonnormally distributed values are expressed as median with 95% confidence intervals. As the populations examined were not independent, Friedman's nonparametric two-way analysis of variance and Wilcoxon signed-rank test were used for comparisons, as appropriate. To evaluate TEE changes under hypothermia, TEE values were normalized by setting the initial value acquired during normothermia at 100% and expressing all subsequent values as % of this value. As the data did not satisfy the normality assumption, the correlation between BEE and TEE values was assessed by means of Spearmann's rank correlation coefficient. Two patients died during the rewarming phase (day 5) due to refractory intracranial hypertension; thus, only eight patients could be studied continuously before, during, and after hypothermia.

Results

Energy expenditure

TEE was 1549 kcal/day (1358–1717) on the day before hypothermia was initiated and significantly decreased to 1099 (939–1296), 1129 (968–1305), and 1157 (989–1325) on the first, second, and third days under hypothermia, respectively (all $p<0.01$, Wilcoxon signed-rank test). No significant differences were evident between the 3 days under hypothermia. TEE increased to 1526 kcal/day (1274–1757) and 1790 (1527–2193) on the first and second days after hypothermia (Fig. 1). This increase was significant as compared to the values acquired under hypothermia (all $p \leq 0.01$, Wilcoxon signed-rank test) but not compared to baseline values. These differences were more pronounced when normalized data for TEE were used: TEE decreased from 100% before induction of hypothermia to 71% (68–76%), 73% (70–79%), and 75% (72–79%) on the first, second, and third days under hypothermia, respectively, and increased again to 99% (95–102) and 116% (108–133) during the following 2 days.

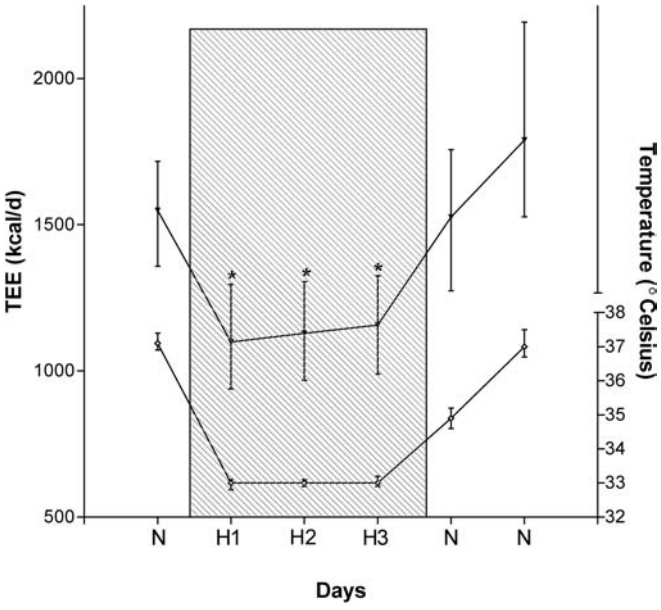

Fig. 1 Total energy expenditure (*TEE*, *above*) and corresponding body temperature (*below*) before hypothermia (admission), during 3 days of hypothermia (*shaded box*), and after hypothermia. *$p<0.01$ vs. during normothermia

A significant correlation between TEE and BEE values was found when values acquired under normothermia were evaluated (Spearmann's rank correlation coefficient $r=0.87$, $p<0.0001$). The discrepancy between TEE and BEE was minimal (103 (26–225)). A significant correlation was also found between TEE and BEE values acquired under hypothermia (Spearmann's rank correlation coefficient $r=0.72$, $p<0.0001$). Still, the discrepancy between TEE and BEE was quite high, with BEE always exceeding TEE values (difference 373 (342–417) or TEE values being 74% (71–77%) of the BEE values).

A statistically nonsignificant increase in respiratory quotient values was noted throughout the study period: 81 (79–83), 82 (78–85), 83 (78–88), 84 (79–89), 86 (81–91), and 89 (82–94) before hypothermia, on days 1–3 under hypothermia and days 1 and 2 after hypothermia, respectively ($p=0.20$, Friedman's analysis of variance).

Clinical parameters

The most frequent complication of MH was pneumonia, observed in nine patients with consecutive antibiotic treatment. Cardiac arrhythmias were seen in six patients: bradycardia (<40 bpm, *n*=3), prolongation of the PR and QT intervals (*n*=3), and ventricular extrasystole (*n*=1). Arterial hypotension as a result of arrhythmia only occurred in one patient who therefore required antiarrhythmic therapy. All patients required catecholamines (norepinephrine and dobutamine) and crystalloid and colloid fluids to maintain mean arterial blood pressure during hypothermia. Thrombocytopenia occurred in three patients (<100,000 platelets/mm^3) but was asymptomatic and did not require specific therapy in any case. Serum potassium concentrations decreased in all patients during MH, whereas levels were lower than 3.5 mmol/l in three patients and required substitution. C-reactive protein values increased from 7 g/l (4–20) before hypothermia to 126 (98–149) on the second day under hypothermia and 133 (107–186) on the first day after hypothermia was terminated. Serum albumin concentration was lower in all patients on day 5 than initial values: 31 g/l (22–34) vs. 36 (28–43) (p=0.07, Wilcoxon signed-rank test).

Discussion

The main result of the present study was the significant reduction in TEE under hypothermia, which ranged at approximately 75% of the baseline values. This finding is in accordance with the study by Tokutomi et al. [8] who reported a reduction in energy expenditure to about 85% of predicted BEE in 15 patients with traumatic brain injury, treated with moderate hypothermia. The mechanisms underlying the reduction in TEE during hypothermia are not fully understood, but downregulation of cerebral and overall metabolism seems to be a major factor [4]. Several studies suggest that metabolic mechanisms which occur along the ischemic cascade are interrupted or at least slowed down by moderate hypothermia [9, 10]. Muscle relaxation could also play a causative role since it is known to markedly decrease energy requirements [11].

Most authors have reported a 10–13% change in energy expenditure per degree Celsius of body temperature [12]. Assuming a linear correlation a decrease in body temperature from 37°C to 33°C would theoretically result in a reduction in energy expenditure of at least 40%, which is higher as that observed in this study. Although we can provide no definitive reason for this discrepancy, it may be at least partially due to the fact that nine of ten patients developed a pulmonary infection, which is known to increase energy demands. The side effects of MH and their frequency observed in our study, particularly pneumonia, cardiac arrhythmias, and hypotension, were in agreement with previous studies in stroke patients treated with MH [6, 13].

A further finding of the present study is the fact that using BEE calculated by the Harris-Benedict equation to predict energy demands of stroke patients treated with MH would result in an overfeeding, as BEE constantly exceeded TEE by approximately 25% during hypothermia. Obviously the sample size of this study prohibits the establishment of clear guidelines concerning patients' energy demands. Still, it appears justified to conclude that BEE is an inadequate tool for estimating caloric needs of acute stroke patients treated with MH, as BEE values are calculated and predicted values rather than real measurements. This conclusion is of particular importance since the risks of overfeeding and hyperglycemia have been documented in several studies [5, 14]. The observed reduction in serum albumin is in accordance with previous study results in other critically ill patients [15]. Possibly, preferential production of acute-phase proteins and hemodilution through extensive administration of high doses of crystalloid and colloid fluids could contribute to this finding.

In conclusion, in sedated, curarized, and ventilated ischemic stroke patients there is a significant fall in TEE during moderate hypothermia. Calculating nutritional needs in these patients by using conventional methods such as BEE may lead to overfeeding. Therefore IC should be used to measure energy expenditure to avoid the complications of hyperglycemia following excessive caloric load.

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