

Comparison between resting energy expenditure measured by indirect calorimetry and metabolic rate estimate based on Harris-Benedict equation in septic patients

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Abstract

Background: Providing an adequate caloric intake is essential for improving clinical outcomes, because inadequate nutrition induces several problems. Previous studies have shown that energy expenditure calculated by classical prediction equations, such as the Harris-Benedict equation (HBE), is greater than the measured resting energy expenditure (REE). To compensate for this discrepancy, additional factors, such as a stress factor, are often used to rescale the value. However, the numerical value of the stress factor, particularly in septic patients, is unknown. Indirect calorimetry (IC) enables to the real-time measurement of REE at the bedside. We hypothesized that the stress factor could decrease over the time course of recovery in septic patients. To test this hypothesis, we measured the REE of septic patients hospitalized in our ICU throughout their intubation period.

Methods: This single-center retrospective study was conducted to compare resting REE measured by IC and the estimated energy expenditure in adult septic patients. Basal metabolic rate (BMR) was estimated by the HBE. Chronological changes in the ratio of measured REE to BMR were analyzed to estimate the stress factor.

Results: A total of 47 patients with sepsis were included in this study. We found that REE/BMR in the septic patients was in the range of 1.07 to 1.11. Moreover, the estimated stress factor did not change over time during the intubation period. REE/BMR did not depend on the number of sedatives administered. Both sequential organ failure assessment (SOFA) scores and blood concentrations of C-reactive protein (CRP) decreased over time. Respiratory quotient (RQ) on the last intubation day was greater than that on the first day.

Conclusions: The REE measured by IC in sedated septic patients was approximately 1.1 times greater than BMR. The ratio of measured REE to BMR does not change with resolution of the illness. This result was likely caused by the concomitant increase in energy intake and improvement in patient general condition at this time. These findings may contribute to better nutrition control in ICU-admitted septic patients.

Introduction

Providing an adequate caloric intake to hospitalized patients is essential for improving clinical outcomes. Overfeeding, for example, could induce several problems, including hyperglycemia, hypercapnia, azotemia, and immune deficiency [1-3]. Therefore, predicting total energy requirements is important for preventing these complications. To predict energy requirements, numerous mathematical prediction equations, such as Harris-Benedict, Schofield, Ireton-Jones, Penn State, and Swinamer equations, have been developed [4-8]. Although the Harris-Benedict equation (HBE) is the oldest of these equations, published in 1919, due to its simplicity it still plays a major role in nutrition management in clinical settings. The HBE was developed based on data collected from a population of healthy volunteers [4]. To apply the HBE to hospitalized patients, additional factors, such as stress and activity factors, are often incorporated into the equation to account for the elevated energy expenditure due to stress or injury [9,10]. As a stress factor for critically ill patients, for example, a value between 1.2 and 1.6 has been chosen in past studies [11-15]. However, few studies have reported on the number that should be used as the stress factor in septic patients [16,17].

Release of proinflammatory cytokines and stress hormones in septic patients results in several metabolic changes, including an increase in energy requirements. The secreted cytokines and stress hormones catabolize skeletal muscle and body fat, and the resultant catabolites are utilized as endogenous energy substrates. Particularly in the early clinical stage of sepsis, an increase in total energy expenditure (TEE) is expected as a result of increase in endogenous energy supply due to enhanced catabolism [18].

Indirect calorimetry (IC) is currently considered the most accurate method for measuring caloric needs [19,20]. IC measures oxygen consumption and carbon dioxide excretion, which are used to calculate

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the respiratory quotient (RQ) and resting energy expenditure (REE), using the Weir equation [21]. We hypothesized that the stress factor in septic patients could be calculated by dividing the value of REE by the basal metabolic rate (BMR) that is calculated using prediction equations.

Further, the stress factor that should be adopted for septic patients could change over the course of the patient's illness, since the total amount of released cytokines and stress hormones depends on the severity of the illness. We hypothesized that the stress factor could become smaller during recovery in septic patients, because REE probably decreases with resolution of the illness. To test this hypothesis, we measured REE in septic patients hospitalized in our ICU and investigated the changes in REE/BMR over the period during which they were intubated.

Methods

Study design

This retrospective observational study was conducted at the intensive care unit (ICU) of Gunma University Hospital. This study was approved by the institutional ethics committee of our facility. Moreover, information was published on the web page of our hospital to inform patients about the study protocol, and give them a chance to refuse inclusion in the study. Adult patients (≥ 18 years of age) admitted to the ICU with a diagnosis of sepsis between April 2010 and March 2015 and who were mechanically ventilated for over three days were included. All the patients included in the study fulfilled the diagnostic criteria for severe sepsis [22,23]. Mechanically ventilated patients who met one or more of the following criteria were excluded: fraction of inspired oxygen (FiO_2) ≥ 0.6 , positive end expiratory pressure (PEEP) > 12 cmH_2O , respiratory rate > 35 breaths/min, and presence of a chest drain with leakage. In addition, patients on hemodialysis or continuous renal replacement therapy were excluded.

Data collection

We measured REE using a mechanical ventilator with an in-built IC (Engström Carestation®, GE Healthcare Japan). This ventilator automatically calculated REE using the Weir equation.

Weir equation [21]

$$\text{REE (kcal/day)} = (3.94 \times \text{VO}_2 + 1.10 \times \text{VCO}_2) \times 1.44 - (2.17 \times \text{UN}^*)$$

VO_2 : oxygen consumption (mL/min), VCO_2 : carbon dioxide production (mL/min), UN: urinary nitrogen excretion (g). * In the Engström Carestation®, the value of UN is fixed at 13 g/day.

$\text{RQ (Respiratory quotient)} = \text{VCO}_2/\text{VO}_2$, was also assessed.

The ventilator with its data migration system enables continuous monitoring of REE. We selected the data measured at 2 a.m. on the first, second, and last days of the intubation period. The protocol required (1) that patients be inactive and undisturbed for 30 minutes before testing and for the 15-minute duration of data collection, (2) an interval of at least 30 minutes between changes in ventilator settings and measurements, and (3) an interval of at least 4 hours between changes in the feeding method and measurements. When the RQ was less than 0.67 or greater than 1.3, we discarded the values and instead incorporated the data obtained as close to 2 a.m. as possible [24-28]. We used any one or more of the following sedatives, as required: propofol, dexmedetomidine, midazolam, and fentanyl (Supplemental

Table S1). Predicted BMR was calculated by either the Harris-Benedict or Schofield equation using actual body weight and height on ICU admission.

Harris-Benedict equation (HBE) [4]

$$\text{Males: BMR (kcal/day)} = 66.5 + 13.8 \times \text{Weight (kg)} + 5.0 \times \text{Height (cm)} - 6.8 \times \text{age}$$

$$\text{Females: BMR (kcal/day)} = 655.1 + 9.6 \times \text{Weight (kg)} + 1.8 \times \text{Height (cm)} - 4.7 \times \text{age}$$

Schofield equation [5]

$$\text{Males: 18-30 years old: } 15.057 \times \text{Weight (kg)} + 692.2, \text{ 30-60 years old: } 11.472 \times \text{Weight (kg)} + 873.1, > 60 \text{ years old: } 11.711 \times \text{Weight (kg)} + 587.7$$

$$\text{Females: 18-30 years old: } 14.818 \times \text{Weight (kg)} + 486.6, \text{ 30-60 years old: } 8.126 \times \text{Weight (kg)} + 845.6, > 60 \text{ years old: } 9.082 \times \text{Weight (kg)} + 658.5$$

We calculated total energy intake from the doctor's order sheet. The decision regarding parenteral and/or enteral nutrition was made by a conference between the attending physician and ICU doctors. REE values measured by IC were not utilized in decision-making. Instead, for the subject with a state of good nutrition, we prescribed mainly enteral nutrients and the total energy intake was gradually increased over time. Whereas, for the subject with a state of poor nutrition, intravenous feeding solution was mainly administered.

Statistical analysis

Data analysis was performed using SigmaPlot 13 (Systat Software, Inc., San Jose, CA) and GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA). Quantitative variables were described as means and standard deviations. Differences between groups were compared using Mann-Whitney U test, paired t-test, one-way ANOVA, or two-way ANOVA post hoc test. $P < 0.05$ was considered significant.

Results

A total of 47 patients with sepsis were included in this study. Their demographic data is shown in Table 1. The patients who survived to discharge only were included, because most moribund patients showed unexpected values of respiratory quotient, within the range adopted as exclusion criteria. We compared REE measured by IC with predicted

Table 1. Patients' demographic data.

Number of patients	47
Male	29 (61.7%)
Age (years)	63 \pm 15 (21-85)
Height (cm)	159 \pm 11 (133-185)
Weight (kg)	56 \pm 17 (30-111)
BMI (kg / m^2)	21.8 \pm 5.4 (11-37)
APACHE score	25 \pm 7 (13-39)
BMR on admission: Harris-Benedict (kcal/day)	1221 \pm 268 (857-2176)
BMR on admission: Schofield (kcal/day)	1289 \pm 251 (930-2145)
Primary site of infection	
respiratory	24
skin and joint	11
abdominal	9
blood stream	1
urinary	2

energy expenditure (as BMR) calculated by the equations mentioned above. As a stress factor, we adopted 1.4-fold rescaling for comparison between measured and predicted energy expenditure, because it has been reported that values between 1.2 and 1.6 should be used as the stress factor for septic patients. In the intubated patients in this study, REE was always smaller than the total energy expenditure (TEE) estimated by 1.4-fold rescaling of the HBE-based BMR (two-way ANOVA with *post hoc* Bonferroni test, $P < 0.0001$), as shown in Figure 1. This was also the case for BMR estimated by the Schofield equation (Figure 1). Since the TEE calculated by Harris-benedict and Schofield equations were not different, we used HBE for further analysis. REE values were plotted against BMR calculated by HBE to determine the stress factor for septic patients (Figure 2). REE and BMR correlated reasonably well on the first day ($R = 0.79$). Additionally, the slope of the graph, namely, REE/BMR, was 1.09. REE also correlated well with BMR on both the second and last days ($R = 0.76$ and 0.78 , respectively). Surprisingly, REE/BMR on the second and last days were 1.07 and 1.11, respectively, suggesting that the estimated stress factor did not change over time (see also Table 2). Many patients in this study were administered some sort of sedative (Table 3, Table S1). However, REE/BMR did not depend on the number of sedatives administered to the patients throughout the intubation period (one-way ANOVA, $P > 0.05$). These results suggest that sedatives had minimal effects on REE/BMR.

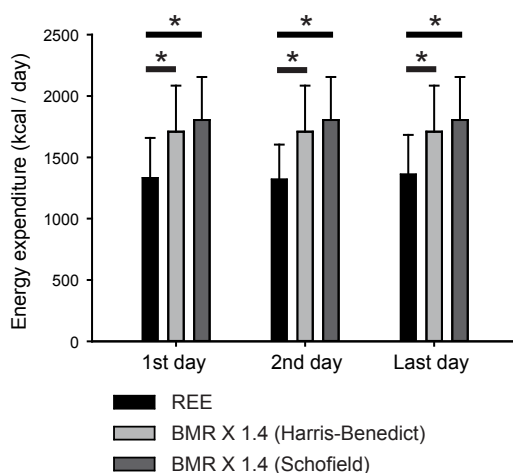


Figure 1. Comparison of the energy expenditure measured by indirect calorimetry (IC) and calculated by Harris-Benedict and Schofield equations. Basal metabolic rate (BMR) was multiplied by 1.4, as a tentative stress factor. Resting energy expenditure (REE) measured by IC was always smaller than estimated total energy expenditure by the prediction equation (two-way ANOVA with *post hoc* Bonferroni test, $P < 0.0001$).

Next, we sought the reasons for the relative constancy of REE/BMR in septic patients during the intubation period. To evaluate the severity of illness, sequential organ failure assessment (SOFA) scores and blood concentrations of C-reactive protein (CRP) were analyzed (Table 2). SOFA scores on the last day were lower than those on the first day (Mann-Whitney U test, $P < 0.001$). This trend corroborates with a decrease in CRP concentrations, suggesting improvement in the general condition of the patients. We also compared total energy intake (Table 2), since that may have impacted REE, and found that total energy intake on the last day was greater than that on the first day (Mann-Whitney U test, $P < 0.001$). Finally, we analyzed RQ and found that RQ on the last day was greater than that on the first day (Mann-Whitney U test, $P = 0.04$). Increased energy intake accompanied with RQ gain suggested that the exogenous energy supplied on the last intubation day was sufficient for the patients.

Discussion

In this study, we found that REE/BMR, i.e., the estimated stress factor, in survivors of sepsis was in the range of 1.07 to 1.11. Moreover, the estimated stress factor did not change over time during the intubation period (Figure 2 and Table 2).

The numerical value of the stress factor that should be multiplied by BMR to predict total energy expenditure in critically ill patients remains controversial. Notably, the optimal number for septic patients is unknown. A previous study that included 73 mechanically ventilated, non-surgical, critically ill patients reported that the measured energy expenditure, namely REE, was no different from that predicted by the HBE, which does not involve multiplication by a stress factor [17]. The authors found that patients with sepsis are an exception to this and concluded that REE was ~1.2 fold higher than that calculated by the unmodified formula during sepsis. Our estimated stress factor in septic patients was relatively small, but did not greatly differ from their data. One possible explanation for the small stress factor was sedation of the subjects. Indeed, it has been reported that REE/BMR decreased significantly by increasing the depth of sedation in postoperative patients [29]. In our study, all patients were intubated and most of them were sedated. However, REE/BMR was not found to be dependent on the number of sedatives administered (Table 3). Besides, patients who did not receive any sedatives might also have been drowsy due to endogenous sedative molecules, such as cannabinoids and ammonia. In other words, the degree of sedation might have been uniform regardless of whether or not sedatives were administered.

The lack of change in REE/BMR over time was likely caused by

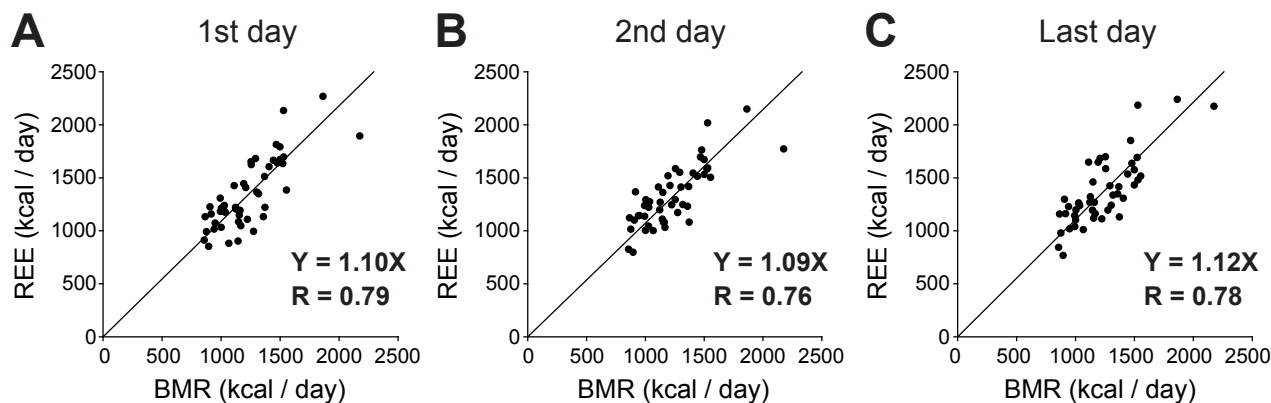


Figure 2. Relationship between resting energy expenditure (REE) and basal metabolic rate (BMR). REE and BMR correlated well on the first, second and last intubation days ($R = 0.79$, 0.76 , and 0.78). The value of REE/BMR was always approximately 1.1.

Table 2. Comparisons of the ratio of measured resting energy expenditure (REE) to basal metabolic rate (BMR), SOFA score, blood concentration of CRP, energy intake, and respiratory quotient between the first and last intubation days. Paired t-test was performed for comparison of REE/BMR. Mann-Whitney U test was used for analyses of the remaining data.

	1st day	Last day	P
REE / BMR	1.10 ± 0.16	1.12 ± 0.17	0.46
SOFA score	10.9 ± 3.0	6.3 ± 3.1	< 0.001
CRP (mg / dL)	14.2 ± 11.2	8.2 ± 6.6	0.02
Energy intake (kcal / day)	448 ± 267	1171 ± 415	< 0.001
Respiratory quotient	0.764 ± 0.08	0.797 ± 0.09	0.04

Table 3. Comparison of the ratios of measured resting energy expenditure (REE) to basal metabolic rate (BMR) on the three days in terms of the number of sedatives used. One-way ANOVA was used for analysis.

	Number of sedatives used			P
	0	1	2 ≤	
1st day	1.17 ± 0.13 (3)	1.06 ± 0.19 (10)	1.10 ± 0.15 (34)	0.60
2nd day	1.18 ± 0.13 (3)	1.11 ± 0.16 (6)	1.08 ± 0.15 (38)	0.52
last day	1.13 ± 0.16 (8)	1.09 ± 0.14 (16)	1.14 ± 0.19 (23)	0.59

following mechanisms. It is known that greater energy intake results in an increase in REE. This was likely the case in this study. The increase in RQ on the last day suggested a shift of the main energy substrate from fats to carbohydrates (Table 2). This shift was also probably caused by the increased energy intake. Conversely, overfeeding on the last day may have resulted in enhanced glycogen and fat synthesis [30]. This is called “nutritional stress”. It has been reported that in the process of glycogen and fat synthesis, 5 and 20%, respectively, of the generated molecules are themselves used up during the process of synthesis [31]. Besides, consumption of glycogen and fat results in an increase in REE. Taken together, excessive energy intake on the last day likely resulted in an increase in REE accompanied by glycogen and fat synthesis. Whereas, decrease in stress hormones, including adrenaline, noradrenaline, cortisol, growth factor and glucagon, resulting from the improvement in the patients’ condition, probably caused a decrease in REE. Stress hormones are released from the adrenal gland or locus ceruleus in the early stages of sepsis, and these induce catabolism of skeletal muscle and fat. Although few studies have shown the effect of stress hormones on energy expenditure, research has shown that exogenous adrenaline and cortisol raise the metabolic rate [32,33]. On the last intubation day, the general condition of the patients in this study had improved significantly, as indicated by the decrease in serum levels of the inflammatory marker, CRP (Table 2). Therefore, we opined that resolution of the illness resulted in a decrease in stress hormones, which in turn led to the decrease in REE. Collectively, an increase in REE caused by the increased energy intake may have been counteracted by a decrease in REE caused by the improvement in the patients’ condition.

Our study has some limitations. This study did not have a specific protocol for nutrition control while the patients were intubated. Therefore, there may have been inter-individual differences in the types of nutrients that were administered to the patients. In theory, measured REE might fluctuate with this uncontrolled factor, because RQ depends on the class of nutrient consumed. To overcome this issue, prospective studies including patients under uniform nutrition control should be performed. Another possible limitation of this study is a small number of measurements per day. Although IC can continuously monitor REE, we adopted data measured at a single time point per day. This protocol was formulated to avert inconstancy in the patient’s condition that can affect REE measurement. Since we did not intend to utilize the data obtained from IC for nutrition control, slight overfeeding

probably occurred in the late intubation period. Despite this, however, we believe that our findings regarding the stress factor in mechanically ventilated septic patients under sedation may contribute to estimation of total energy expenditure using prediction equations.

Conclusions

The measured REE by IC in septic patients under sedation was approximately 1.1 times greater than BMR. The ratio of measured REE to BMR does not change with resolution of the illness throughout the intubation period. This result was likely caused by the concomitant increase in energy intake and improvement in patient general condition at this time. These findings may contribute to better nutrition control in septic patients in the ICU.

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Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

All the authors participated in data collection. JK designed and conducted the study. JK and TT wrote the manuscript. FK and SS supervised the study. All the authors read and approved the final manuscript.

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