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Original Article

Resting energy expenditure in non-ventilated, non-sedated patients recovering from serious traumatic brain injury: Comparison of prediction equations with indirect calorimetry values

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S U M M A R Y

Background & aims: Little is known about energy requirements in brain injured (TBI) patients, despite evidence suggesting adequate nutritional support can improve clinical outcomes. The study aim was to compare predicted energy requirements with measured resting energy expenditure (REE) values, in patients recovering from TBI.
Methods: Indirect calorimetry (IC) was used to measure REE in 45 patients with TBI. Predicted energy requirements were determined using FAO/WHO/UNU and Harris–Benedict (HB) equations. Bland–Altman and regression analysis were used for analysis.
Results: One-hundred and sixty-seven successful measurements were recorded in patients with TBI. At an individual level, both equations predicted REE poorly. The mean of the differences of standardised areas of measured REE and FAO/WHO/UNU was near zero (-9 kcal) but the variation in both directions was substantial (range -591 to $+573$ kcal). Similarly, the differences of areas of measured REE and HB demonstrated a mean of 1.9 kcal and range -568 to $+571$ kcal. Glasgow coma score, patient status, weight and body temperature were significant predictors of measured REE ($p < 0.001$; $R^2 = 0.47$).
Conclusions: Clinical equations are poor predictors of measured REE in patients with TBI. The variability in REE is substantial. Clinicians should be aware of the limitations of prediction equations when estimating energy requirements in TBI patients.

1. Introduction

Patients sustaining a serious moderate to severe traumatic brain injury (TBI) often require long periods of hospitalisation involving intensive care and rehabilitation.

Severe metabolic disturbances have been observed in patients sustaining a serious TBI. The systemic effects of the metabolic response to head injury include: increased energy demands; increased protein turnover; a hyperdynamic cardiovascular state; impaired glucose metabolism; altered mineral and trace element status; increased cytokine and hormonal release and altered gastrointestinal function. The systemic effects of this metabolic response, if they remain unchecked, can increase the risk of secondary complications in patients with TBI and ultimately increase mortality.

Nutritional intervention can play an important role in reducing the risk of developing secondary complications. A review by the Cochrane Collaboration concluded that early nutritional support may be associated with a trend towards better outcomes in terms of survival and disability in this patient group.[1] More recent work demonstrated that patients who were not fed within 5 and 7 days after TBI had a two- and four-fold increased likelihood of death.[2] However, the provision of adequate nutritional support to meet individual energy demands is often challenging in practice. This is largely due to the uncertainty regarding actual energy requirements in this clinical group.

Traditionally in clinical practice, energy requirements are calculated using prediction equations, validated for use mainly in healthy populations. A stress or injury factor is often applied depending on the estimated degree of metabolic response to injury. A further factor may be applied to encompass physical activity level

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and diet induced thermogenesis to provide an overall estimate of total energy requirements.

In patients with brain injury, there is considerable variability in measured REE in the first 2 weeks of injury, with some patients yielding measured REE at near normal values and some patients demonstrating extreme hypermetabolism, up to 100% above normal calculated values.[3–5] The reported variability has been attributed to the effects of sedation, barbiturate therapy, steroid treatment, mechanical ventilation, diet induced thermogenesis and/or infection. Patients receiving sedatives and or muscle relaxants were found to have a mean measured REE 30% lower than those patients not receiving sedation or in barbiturate coma.[6–8] Current guidelines for nutrition in TBI recommend replacing 140% of the REE in non-paralyzed patients and 100% in paralyzed patients by the seventh day of injury.[9]

Research to date provides little information regarding REE in head injured patients after 2 weeks, typically when ventilation and sedation has been stopped and patients are in various degrees of consciousness and breathing spontaneously. There is also little information regarding the factors determining energy requirements in the later stages of trauma in this complex patient group.

The main aim of this study was to compare predicted REE values, using the equations of Harris–Benedict and FAO/WHO/UNU in a group of non-sedated, non-ventilated patients recovering from TBI, with indirect calorimetry values using the methods comparison analysis described by Bland and Altman.[10] A second aim of this study was to determine factors that can predict REE in this patient group.

2. Materials and methods

Forty-five patients with an isolated traumatic brain injury (TBI), were recruited from the Regional Neurosurgical Unit at The Royal Group of Hospitals, Belfast, between January 2005 and June 2006. All patients were breathing spontaneously and were not receiving sedation. The study was given ethical approval from the NHS Research Ethics Committee, Northern Ireland. Informed consent was provided by the patients' next of kin.

2.1. Subjects

All patients had a glasgow coma score (GCS) ≤ 11 on admission and were severely brain injured but were not pronounced brain dead. They were haemodynamically stable without clinically significant additional trauma other than the brain injury. All patients were receiving $\leq 40\%$ supplementary oxygen and were not sedated or artificially ventilated.

2.2. Measurements

Each patient underwent repeated daily measurements of resting energy expenditure (REE) and nutrition assessment for approximately 7–9 days after sedation and artificial ventilation were stopped. All metabolic and nutritional assessments were conducted by the same observer between 10.00 and 14.00 h in a ward environment with an ambient temperature of 25 °C. The patient lay in a recumbent position following a 4-h fast and with no nursing, medical or therapist intervention for 1 h prior to the measurement time. Weight was measured using hoist scales (opera hoist scales, Argo ltd, Gloucester.UK) at least 1 h prior to the measurement time and recorded to the nearest 0.1 kg. Length was measured with a tape measure while the patient was in the recumbent position without footwear. Length was recorded to the nearest centimetre. Body mass index (BMI) (kg/m^2) was calculated as weight (kg)/height^2 (m). Clinical information including demographics

diagnosis, surgical intervention, days since injury, drug treatments, body temperature (°C), GCS, concentration of supplementary oxygen (%) and route of nutritional support were recorded.

2.3. Measurement of resting energy expenditure (REE)

Indirect calorimetry (IC), a measure of minute-by-minute carbon dioxide production (VCO_2) and oxygen consumption (VO_2), via an open ventilated hood system was used to measure REE. A Deltatrac II (Datex-Ohmeda, Helsinki, Finland) portable IC was used with all patients. The gas analysers within the Deltatrac were calibrated using Quickcal with the concentration of 95% oxygen, 5% carbon dioxide (Datex-Ohmeda, Helsinki, Finland) prior to each measurement. A flow calibration to assess the overall performance of the system was carried out every 6 months. A standard protocol was used by the investigator when operating the IC.

If the patient required supplementary oxygen, a supplementary oxygen kit (Datex-Ohmeda, Helsinki, Finland) was attached to the Deltatrac II. The supplementary oxygen was allowed to flow through the system for approximately 20 min prior to the measurement time. A ventilated hood was placed over the patient's head and neck. For those patients requiring supplementary oxygen, an elastic seal was attached to the canopy to ensure there were no leaks around the tracheostomy site. The respiratory gases were collected up to 60 min. Steady state (SS) conditions were defined as five, four or three consecutive minutes of data where the coefficient of variation (CV) was $\leq 10\%$ for VCO_2 and VO_2 values, $\leq 5\%$ for RQ and the RQ value was in the physiologic range of 0.67–1.3. The patient's oxygen saturation levels were continually monitored during the measurement time using an oxygen pulsimeter (Welch–Allyn 52000 series, Welch–Allyn, USA). Minute-by-minute measurements of VCO_2 (ml/min), VO_2 (ml/min), RQ (VCO_2/VO_2) and FiO_2 (%) were downloaded to a COLLECT software programme (Datex-Engstrom Division, Helsinki, Finland) when the measurement time had ended.

Measured REE (MREE (kcal/day) was calculated using the abbreviated Weir equation.[11]

$$REE = ((VO_2(3.941) + VCO_2(1.106)) \times 1.44$$

VCO_2 and VO_2 were measured in millilitres (ml) per minute and REE measured in kilocalories per day.

2.4. Prediction equations

The prediction equations used to estimate REE in all subjects are shown in Table 1. These were the most widely used equations of Harris–Benedict and FAO/WHO/UNU. These regression equations use simple variables of age, gender, weight and/or height to estimate REE as shown in Table 1[12–13]

2.5. Statistical analysis

Statistical analysis was conducted using the SPSS for windows version 12.0.1 (SPSS, Chicago, IL, USA). Normally distributed continuous variables are described as mean $\pm$ SD unless otherwise

Table 1
Equations used to predict REE in clinical practice.

Author(s)	Equation for REE (kcal/day)
Harris–Benedict (HB)[12]	Men = 66 + 13.75(wt) + 5.0(ht) − 6.76 (age)
	Women = 665 + 9.56(wt) + 1.85(ht) − 4.68(age)
FAO/WHO/UNU[13]	
Age 18–29 years	Men = 15.1(wt) + 692: women = 14.8(wt) + 487
Age 30–59 years	Men = 11.5(wt) + 873: women = 8.3(wt) + 846
Age 60–74 years	Men = 11.9(wt) + 700: women = 9.2(wt) + 687

Wt, weight (kg); ht, height (cm).

stated. A p value of <0.05 was considered statistically significant. Descriptive statistics were used to describe the subject population. Each patient's serial measurements were summarised using the area under the curve. A student's t-test was used to assess agreement between mean predictive values and mean measured REE. The Bland–Altman method was used to assess agreement between the standardised areas of measured values and predicted values. Multiple weighted regression analyses were used to evaluate the relationship between the explanatory variables and measured REE in the study sample.

3. Results

3.1. Patient demographics

A total of 210 repeated IC measurements were recorded for 45 patients recruited into the study. Of these measurements 43 (20.5%) were unsuccessful resulting in 167 successful IC measurements. Of the 45 patients recruited into the study, three patients failed to yield any successful measurements. Therefore the subsequent analysis was based on data from 42 patients. The patient characteristics are shown in Table 2.

All 42 patients had a serious traumatic brain injury with a mean admission GCS score of 6.2 (range 3–11) and were not receiving artificial ventilation or sedation upon inclusion into the study. The cause of TBI in our patient population was as a result of: falls ($n = 22$); road traffic accidents ($n = 13$); assaults ($n = 4$); quad bicycle accidents ($n = 2$); and gunshot wounds ($n = 2$). Sixty-nine percent ($n = 29$) of our patient population underwent neurosurgery. All patients spent variable lengths of time in the Regional Intensive Care Unit (RICU) at the RVH prior to transfer to the Regional Neurosurgical Unit (RNU). The mean length of time from injury to the first metabolic measurement was 21 days (range 5–67 days).

Using the World Health Organization (WHO) classification of BMI (kg/m^2), 29% of our study population were considered underweight (BMI < 18.5), 58% were considered normal weight (BMI 18.5–24.99), 9.6% were considered overweight (BMI 25–29.99), and 3% were considered clinically obese (BMI > 30). Forty patients in the study sample had repeated weight measurements. Eighty-five percent of these patients experienced weight loss ($n = 34$) within the study time. The mean weight loss was 2 kg (range 0.1–10 kg; SD 2.13) over a mean 5.5 days (range 1–11 days; SD 2.7). The majority of patients at the time of measurement required enteral nutrition support: 58% required nasogastric feeding; 4% required

supplementary nasogastric feeding in addition to oral diet; 3% received nutrition support via a percutaneous endoscopic gastrostomy (PEG) tube; oral diet was consumed by 34% of our patient group whilst 1% was nil orally without feeding access. A 4-h fast, prior to the measurement time, was observed for all patients included in the study. The mean prescribed kilocalorie intake for patients requiring enteral nutrition support was 2295 kcal/day.

Each of the 42 patients had a mean of four successful metabolic measurements (range 1–9) at variable lengths of time after the initial injury. Mean GCS at the time of measurement was 11 (range 4–15). Approximately 53% of our patient group required supplementary oxygen via percutaneous tracheostomy to maintain oxygen saturations. Therefore a strict IC measurement protocol as described in Section 2 was observed for these patients. Oxygen saturations in addition to concentration of inspired oxygen (FiO$_2$) were continually monitored throughout the measurement time by a trained investigator. Furthermore, only data meeting predefined SS conditions was used for data analysis. SS conditions were met in all successful measurements with a mean RQ value of 0.86. Of the 167 successful measurements, 133 (80%) achieved 5-min SS conditions, 18 (11%) achieved 4-min SS conditions and 16 (9%) achieved 3-min SS conditions. Twenty percent of all metabolic measurements recorded were unsuccessful.

3.2. Agreement between measured REE and predictive values (kcal/day)

Mean measured REE was 1588 kcal/day (SD 446 kcal/day). Fig. 1 illustrates the serial mean measured REE over time (days since injury) for each of the 42 patients with successful IC measurements. However, in order to compare the measured REE with the FAO/WHO/UNU and HB prediction values at a group and individual level it was necessary to summarise serial sets of repeated measurements for individual patients since each patient had varying time intervals between measurements of REE. Each patient set was summarized by its standardized area under the line graph of measurement against time (days). Area under the curve (AUC) is a standard method of summarizing serial observations; this area was divided by the time interval in days from the first measurement to the final measurement to give the standardized area (kcal/day). The mean within patient CV was calculated for 42 patients with two or more measurements as 11% (SD 8.2; range 0–43%). The analyses of the AUC data were based on 40 patients; two patients with measured REE CV values exceeding 30% were excluded (the results were considered to be unreliable). The mean within patient CV was 10% (SD 5.6; range 0–21%) when the two patients with CV exceeding 30% were excluded.

Table 2
Patient characteristics of 42 patients with a serious traumatic brain injury.

Patient characteristic ($n = 42$)	Mean (SD) range
Age (years)	35.6 (14.6) 17–65
Male/female	28/14
Admission GCS	6.2 (2.4) 3–11
Measurement GCS	11 (2.85) 4–15
Time since injury (days)	21.1 (11.6) 5–67
Weight (kg)	61.9 (14.0) 36.5–127
Height (cm)	170.5 (10.3) 152–190
Body mass index (kg/m^2)	21.2 (3.7) 15.0–35.9
Body temperature (°C)	36.8 (0.6) 35.5–38.8
Measured REE (kcal/day)	1588 (445.6) 910–4364
FAO/WHO/UNU REE (kcal/day)	1512 (237.4) 1024–2610
HB REE (kcal/day)	1497 (234.8) 1012–2570
VCO$_2$ (ml/min)	191 (48) 119–479
VO$_2$ (ml/min)	225 (62.9) 127–634
RQ	0.86 (0.10) 0.69–1.19

GCS, Glasgow comma score; VCO$_2$, carbon dioxide production; VO$_2$, oxygen consumption; RQ, respiratory quotient.
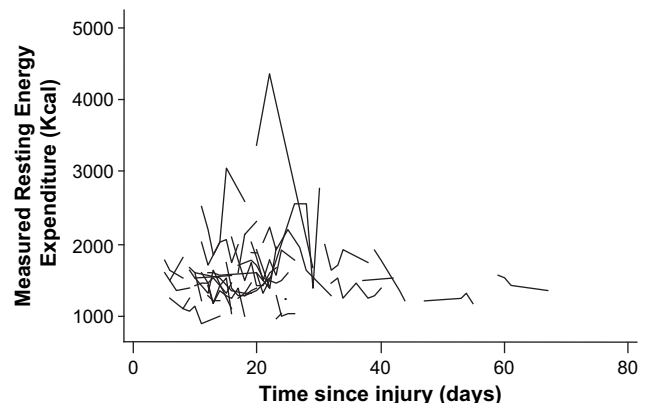
Fig. 1. Individual plots of mean measured REE (kcal/day) over time (days since injury) for 42 patients recovering from serious TBI.

Using a paired students *t*-test, there were no significant differences at a group level between the standardized areas for measured REE and predicted FAO/WHO/UNU values ($p = 0.84$); the standardized areas for measured REE values and the standardized areas for predicted HB values ($p = 0.97$) and the FAO/WHO/UNU prediction values and HB prediction values ($p = 0.44$).

To assess agreement at an individual level the Bland–Altman method was used. This method involves plotting the differences of the standardized areas for measured REE and is based on the predicted values for each patient against the average of these areas for each patient. The limits of agreement were defined as the mean difference ± 2 SD of the mean differences between the measured REE and each of the prediction equations. The mean standardized area measured REE was 1510 kcal/day (SD 308 kcal/day). This is approximately 5% different from the calculated mean measured REE. However, it was necessary to use the standardized value for statistical analysis due to the variability in measured REE over variable periods of time for each individual patient. The level of agreement at ±10% of the mean measured area REE was used to explore clinically acceptable limits of agreement between the measured REE values and the predicted values.

Bland–Altman plots (Figs. 2 and 3) for both predictive equations and measured REE indicate good agreement at the mean difference ± 2 SD of the differences limits of agreement. Approximately 95% of predictive values were within these limits of agreement for the FAO/WHO/UNU equation and 97.5% for the HB equation. However, these limits of agreement were very wide in both directions, greater than ±550kcal/day, which was considered not to be clinically acceptable. Hence, limits of agreement were also considered at the ±10% of mean measured REE (±151 kcal/day). Both equations indicated poor agreement with measured REE at this level. The FAO/WHO/UNU prediction demonstrated 50% agreement at the ±10% limit of agreement with approximately 22.5% differences greater than 10% of the mean measured REE

and 27.5% of differences below 10% of the mean measured REE values. The HB produced similar results with 45% of predicted values within ±10% of measured REE with 30% of differences greater than 10% and 25% of differences less than 10% of mean measured REE.

3.3. Regression analyses

The purpose of these analyses is to investigate the relationships between measured REE measurements and clinically obtained variables including GCS, patient status during the measurement of REE (whether the patient was awake (eyes open) or asleep (eyes closed), age (years), time since injury (days), gender, supplementary oxygen concentration (%), temperature (°C), antibiotic treatment, weight (kg), height (cm) and BMI (kg/m^2).

The data consists of 167 records of the measurements/observations of the above variables from 42 patients; there was complete information on the above variables. Repeated measurements of a patient cannot be considered independent and as such should be analysed in an appropriate manner. Instead of analysing at the patient level, the unit of analysis is the "state" of a patient defined by the pair (GCS, patient status, i.e. awake or asleep) – from initial analysis it was found that these two variables have a significant effect on measured REE. This means that a patient may provide data for several states, e.g. patient 2 has two records for state (GCS 9, awake) and two records for state (GCS 10, awake). Where a patient has several records for a given state, the data in these records are averaged to give a mean record with weight equal to the number of records averaged. The frequencies of the numbers of records per state are shown in Table 3, e.g. 64 states had a single record, 26 states had two records, etc.

This process gave a set of 105 mean records which were analysed using weighted multiple regression modelling with the weights as described above, the dependent variable being
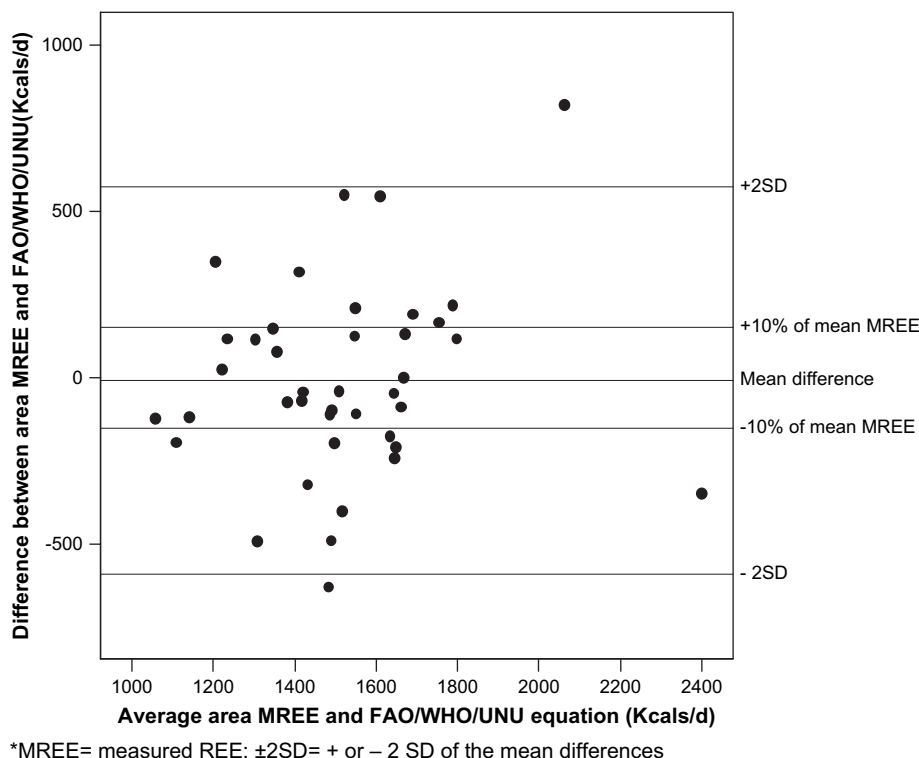

*MREE= measured REE; ±2SD= + or − 2 SD of the mean differences

Fig. 2. Bland–Altman plot showing agreement between the standardized areas of measured REE and FAO/WHO/UNU predicted REE (kcal/day) in 40 patients with serious TBI.
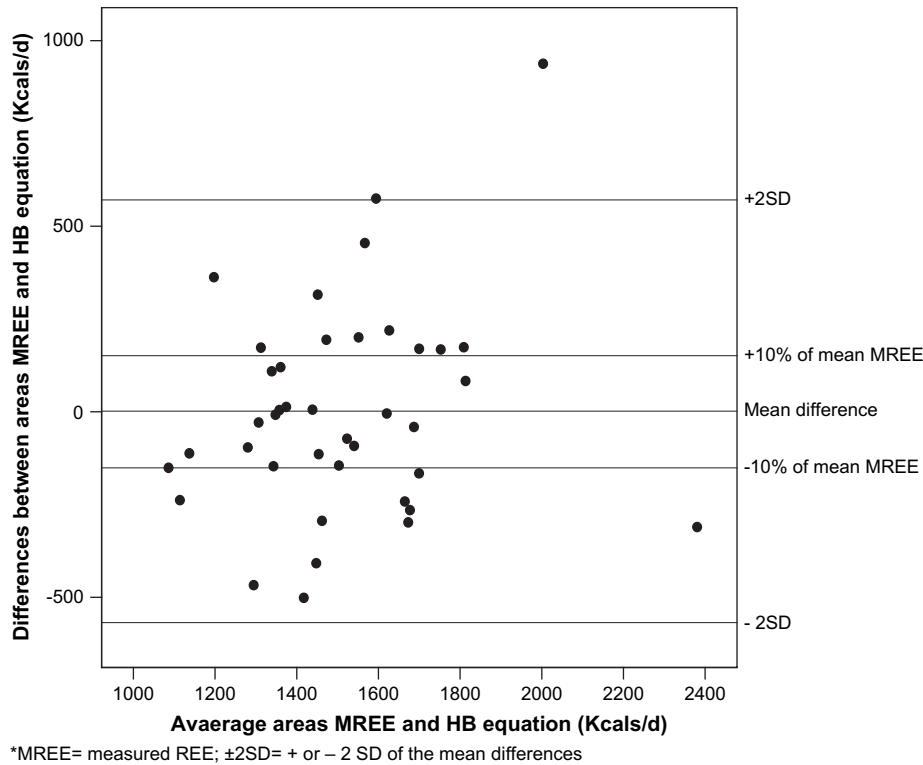
*MREE= measured REE; ±2SD= + or − 2 SD of the mean differences

Fig. 3. Bland–Altman plot showing agreement between the standardized areas of measured REE and HB predicted REE (kcal/day) in 40 patients with serious TBI.

measured REE, the explanatory variables being the remaining variables listed above.

In the regression model with explanatory variables GCS and patient status and their interaction, the interaction is non-significant at the 5% level ($p = 0.23$) and therefore was not included in the subsequent models.

In the basic regression model, with explanatory variables GCS and patient status, both GCS ($p < 0.001$) and patient status ($p < 0.001$) had very highly significant effects on measured REE (R^2 0.25). Estimated mean measured REE decreased by 59 kcal for a one unit increase in GCS, independently of patient status. Estimated mean measured REE for patient status when awake is 319 kcal greater than estimated mean measured REE for patient status when asleep, independently of GCS. All subsequent models will contain GCS and patient status.

Regression models including GCS, patient status and each of the remaining variables were fitted. Age ($p = 0.61$), time since injury ($p = 0.58$), supplementary oxygen concentration ($p = 0.28$) and antibiotic treatment ($p = 0.69$) were found to be non-significant predictors of measured REE and were not included in subsequent models. Each of the other explanatory variables was found to have a significant effect on measured REE. Using a cut off value of 0.2 for the p values, the following explanatory variables were considered

in the multivariable regression modelling: GCS; patient status; BMI; gender; temperature; weight; and height.

Variable selection by backward elimination removed gender ($p = 0.87$) and weight ($p = 0.84$) to give the model:

GCS $B = −51$ ($p < 0.001$); patient status $B = 330$ ($p < 0.001$); temperature $B = 141$ ($p = 0.014$); BMI $B = 40$ ($p < 0.001$); height $B = 11$ ($p = 0.001$). $R^2 = 48\%$.

A further similar model is presented where variable selection by backward elimination removed gender ($p = 0.94$) and BMI ($p = 0.98$) from the multivariable model to give the model shown in Table 4. This was the preferred model as fewer clinically obtained variables are required for the estimation of REE (kcal/day) in clinical practice. This model shows that estimated mean measured REE decreases by 50 kcal for a one unit increase in GCS independent of the other variables. Mean measured REE is 330 kcal greater when the patient status is recorded as awake rather than asleep when adjusted for the effects of the other variables. Similarly, there is a 144 kcal increase in estimated mean measured REE for a 1 °C increase in temperature and an increase of 14 kcal for a 1 kg increase in weight when adjusted for the effects of other variables. This final model gives an R^2 value of 47%.

Table 3
Frequencies of the numbers of records per patient state defined by GCS and patient status during 167 IC measurements in 42 patients with TBI.

Number of records per state	Frequency
1	64
2	26
3	10
4	4
5	1
Total	105

Table 4
Multivariable regression analysis showing the effect of significant explanatory variables on measured REE measurements in patients with a TBI.

Variable	Coefficient B	p value	95% Confidence interval for B	
			Lower bound	Upper bound
Constant	−4166	0.05	−8414	81
GCS	−50	<0.0001	−73	−28
Patient status	330	<0.0001	204	466
Temperature	144	0.013	31	256
Weight	14	<0.0001	10	19

3.4. Final model

Measured REE $(kcal/day) = -4166 - 50GCS + 330$ patient status $(1,eyes\ open;\ 0,eyes\ closed) + 144$ temperature $(°C) + 14$ weight (kg)

4. Discussion

The HB equations and/or FAO/WHO/UNU equations are applied to both healthy populations and clinical populations worldwide to estimate basal energy requirements. The limitations of these equations are frequently unrecognized and they are often applied injudiciously at the individual level for both patients and healthy volunteers. Other authors have questioned the accuracy of the both the HB and FAO/WHO/UNU equations in healthy, obese and clinical populations.[14–16] Our results in patients recovering from brain trauma add to the growing weight of scientific research questioning the validity of these prediction equations. We found that the HB and FAO/WHO/UNU equations correctly predicted resting energy requirements within 10% of the measured values in approximately 50% of cases. Previous studies evaluating predicted values and measured REE in various clinical populations have used a limit of agreement at ±10% of the mean measured REE. It has been assumed in the literature that hypermetabolism in clinical populations is defined as 10% or more above predicted REE and hypometabolism as 10% or more below predicted REE.[17] Interestingly, approximately 25% of measured values in our patient group demonstrated a hypermetabolic state whereas 25% demonstrated a hypometabolic state. These results are consistent with measured REE in other clinical populations such as surgical patients and critically ill patients.[17–19] Data from critically ill patients have shown that approximately 35–65% demonstrate a classic hypermetabolic response, 30–50% showing a normometabolic pattern and a further 15–20% having a hypometabolic response.[19] The significance of a hypometabolic response in critically ill patients is not clear. However, in other clinical groups at some point the hypermetabolic response to trauma subsides as the patient recovers. Weight loss and malnutrition per se can reduce REE by up to 40%.[20–22] In our study, 29% of the study group were initially clinically underweight with 85% of patients experiencing further weight loss during the study period. This may have contributed to the variability in measured REE in our study sample.

Until now, little data existed regarding REE in patients greater than 2 weeks post severe brain injury. Studies to date have produced conflicting results in only small numbers of brain injured patients.[3,23] Additionally, the majority of research investigating REE in brain injured patients was conducted 10–20 years ago. There have been advances in medical, surgical and rehabilitation treatment since this time which may influence REE measurements. We have reported our results in a significantly larger group of seriously brain injured patients who are representative of the normal clinical population. The results indicate that REE is highly variable in patients recovering from TBI. The mean within patient variability was recorded as 11% (range 0–43%) which is similar to recorded variability in measured REE in other clinical populations such as critically ill patients.[19,21,22] This is in contrast to healthy individuals where the reported normal day-to-day variation of measured REE is approximately 3–6%.[22,24–25]

The demonstrated differences between the measured and predicted values in our patients recovering from TBI are multifactorial and include the effects of measurement error, investigative error and biological variation. We minimised measurement error by employing an evidence-based standardised protocol for the operation of the metabolic monitor, using one trained investigator to perform all metabolic measurements and rigorously analysing the data using predetermined steady state criteria for analysis. Hence, over 20% ($n = 43$) of metabolic measurements in this study were unsuccessful. It would have been impossible to conduct IC measurements for longer than 60 min in this patient group due to the unstable nature of the clinical condition, frequent need for therapy intervention, medical support and investigations over a 24-h period. Despite our efforts to minimise measurement error, there are accuracy and precision errors associated with the IC calorimeter and procedure which have been reported as less than 5%, when the same calorimeter is used.[25,26]

Biological variation in REE during the first 2 weeks of brain injury have been attributed to the effects of sedation, barbiturate therapy, steroid treatment, mechanical ventilation, diet induced thermogenesis, days since injury, severity of injury, body temperature, abnormal motor activity and/or infection, which can independently serve to increase or decrease measured REE.[3–9,21,22]

To our knowledge, this is the first study investigating factors contributing to measured REE in a larger group of patients recovering from TBI when sedation and ventilation have been discontinued. We demonstrated that the severity of brain injury continues to affect the energy expenditure of patients in the later stages of trauma recovery. We also showed that REE is significantly higher when the metabolic measurement is performed in brain injured patients when eyes were noted to be open during the steady state. This is probably related to the stimulation of both the CNS and sympathetic nervous system with concomitant increase in muscle tone. Wakefulness has been described as a complex process with not only stimulation of CNS activity but increased autonomic activity and sympathetic nervous system activity with release of catecholamines from the adrenal medulla.[27] In clinically stable hospitalized patients and critically ill mechanically ventilated patients these factors have resulted in a 10% increase in energy expenditure.[21,22] Wakefulness resulted in a mean 22% increase in energy expenditure in our patient sample. One possible explanation for the differences in the results obtained is the direct effect of the brain injury itself on the regulation of the complex processes governing wakefulness. There is some evidence that arousal changes in the damaged brain are altered, suggesting control mechanisms have been lost or damaged, compared with the normal brain.[27] Additionally, hypocretin-1, involved in the regulation of the sleep–wake cycle, was found to be abnormally low in 95% of 44 patients with acute TBI suggesting some degree of hypothalamic damage.[28] Body temperature was also a significant contributor, but not the main determinant, of the overall variability in measured REE in our study sample. We found an average 9.5% increase in REE for each measured degree centigrade rise in temperature. This agrees with previous research in other clinical groups where REE increased by 6–13% for each degree centigrade rise in temperature.[22,29]

Body size is one of the biggest determinants of REE in humans. We found that body weight was a significant contributor to the overall variability in measured REE in our study sample. This is unsurprising since the majority of prediction equations used today to estimate REE in clinical populations include body weight as a variable. Body weight alone explained up to 75% of the variance in REE in the original HB regression equations.[30] However, we found that body weight alone explained only 19% of the variation in measured REE in our study sample. The ability of the multiple variables (GCS, patient status (eyes open or eyes closed), temperature and weight) to estimate REE in spontaneously breathing, nonsedated patients in the latter stages of serious TBI was only fair. Over 50% of the variance in measured REE remains unaccounted for. Clearly, there are factors not identified in our study that will determine REE in this patient group. Further study of body composition and fat free mass, hormonal status, sympathetic

nervous system activity, the effects of hypertonicity and posturing and putative autonomic dysregulation may yield additional information regarding the variation in measured REE in this patient group. Furthermore, to facilitate the provision of adequate nutritional support to patients recovering from TBI, knowledge of total energy needs is important. The overall effect of physical activity and dietary induced thermogenesis on total energy needs in patients recovering from TBI is uncertain. Further research is warranted using high quality tracer techniques, such as bicarbonate–urea or doubly labelled water in combination with indirect calorimetry, to investigate the extent of total energy requirements in this complex group.

5. Conclusion

Due to the variable nature of measured REE in patients recovering from brain injury reliance on currently available prediction equations can lead to serious errors in the calculation of REE. Currently, it may be necessary to measure individual REE using the technique of IC in clinical practice, to help guide the provision of adequate nutritional support.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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