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Original

Basal Energy Expenditure measured by indirect calorimetry in patients with squamous cell carcinoma of the esophagus

Camila Beltrame Becker Veronese[1], Léa Teresinha Guerra[2], Shana Souza Grigolleti[3], Juliane Vargas[4], André Ricardo Pereira da Rosa[5] and Cleber Dario Pinto Kruel[6]

[1]MSc in Gastroenterology and Hepatology - UFRGS. [2]MSc in Gastroenterology and Hepatology - HCPA, UFRGS. [3]MSc in Cardiology - UFRGS. [4]Graduate in Medicine - HCPA, UFRGS. [5]Doctor in Surgery - UFRGS. [6]PhD in Surgery - FAMED, UFRGS

Abstract

Background: **Determination of Basal Energy Expenditure (BEE) is essential for planning nutritional therapy in patients with esophageal cancer. Aims: The objective of this study was to determine BEE through indirect calorimetry (IC) in patients with squamous cell carcinoma of the esophagus (SCC).**

Methods: **Cross-sectional study involving 30 patients admitted with a diagnosis of SCC who underwent IC before starting cancer therapy. The BEE was evaluated using IC and also estimated by means of the Harris-Benedict Equation (HBE). Nutritional assessment was conducted using anthropometric parameters (body mass index, arm circumference, triceps skinfold thickness, arm muscle circumference, and weight loss), biochemical parameters (albumin, transferrin and C-reactive protein) and tetrapolar bioimpedance to assess body composition (fat free mass). Additionally, lung capacity was measured and clinical staging of the cancer established by the TNM method.**

Results: **The mean of the BEE for IC and Harris-Benedict Equation were 1421.8 ± 348.2 kcal/day and 1310.6 ± 215.1 kcal/day, respectively. No association was found between BEE measured by IC and clinical staging (p=0.255) or the Tiffeneau Index (p=0.946). There were no significant associations between BEE measured by IC and altered dosages of transferrin, albumin and C-reactive protein (p=0.364, 0.309 and 0.780 respectively). The factors most associated with BEE were BMI and fat free mass.**

Conclusion: **The BEE of patients with SCC was underestimated when using the HBE, and the result overestimated when incorporating an injury factor with the HBE. Therefore, despite the practical difficulties of implementing IC, its use should be considered.**

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Correspondencia: Camila Beltrame Becker Veronese.
Rua Dona Augusta, 180/502.
90850130 Porto Alegre/RS.
E-mail: mila.becker@gmail.com

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EL GASTO ENERGÉTICO BASAL MEDIDO POR CALORIMETRÍA INDIRECTA EN PACIENTES CON CARCINOMA DE CÉLULAS ESCAMOSAS DEL ESÓFAGO

Resumen

Antecedentes: **La determinación del gasto energético basal (GEB) es esencial para la planificación de la terapia nutricional en pacientes con cáncer de esófago.**

Objetivos: **El objetivo de este estudio fue determinar GEB por calorimetría indirecta (CI) en pacientes con carcinoma de células escamosas del esófago (CCS).**

Métodos: **Estudio transversal con 30 pacientes ingresados con el diagnóstico de CCS que se sometieron CI antes de iniciar la terapia contra el cáncer. La abeja se evaluó con CI y estimó por medio de la ecuación de Harris-Benedict (EHB). La evaluación nutricional se realizó utilizando los parámetros antropométricos (índice de masa corporal, circunferencia del brazo, el pliegue del tríceps, circunferencia muscular del brazo y pérdida de peso), parámetros bioquímicos (albúmina, transferrina y la proteína C-reactiva) y bioimpedancia tetrapolar para evaluar la composición corporal (grasa masa). Además, la capacidad pulmonar se midió y la estadificación clínica del cáncer establecido por el método TNM.**

Resultados: **La media de la abeja para la ecuación CI y Harris-Benedict fueron 1421,8 ± 348,2 kcal / día y 1310,6 ± 215,1 kcal / día, respectivamente. No se encontró asociación entre GEB medido por CI y la estadificación clínica (p = 0,255) o el Índice Tiffeneau (p = 0,946). No se encontraron asociaciones significativas entre GEB medidos por dosis de CI y alteración de la transferrina, albúmina y proteína C reactiva (p = 0,364, 0,309 y 0,780, respectivamente). Los factores más asociados con GEB fueron el IMC y la masa libre de grasa.**

Conclusión: **La abeja de los pacientes con CCS fue subestimada cuando se utiliza el EHB, y el resultado sobreestimado cuando se incorpora un factor de daño con el EHB. Por lo tanto, a pesar de las dificultades de aplicación práctica de CI, su uso debe ser considerado.**

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Palabras clave: *Cáncer de esófago. Calorimetría indirecta. El gasto energético basal.*

Abbreviations

BEE: Basal Energy expenditure.
IC: Indirect Calorimetry.
HBE: Equação de Harris-Benedict.
SCC: Squamous cell carcinoma.
BMI: Body Mass Index.
CRP: C-reactive protein.
FFM: Fat Free Mass.

Introduction

Basal Energy Expenditure (BEE) is the main contributor to total energy expenditure (60% to 75%) and corresponds to the energy expenditure over a 24 hour period used for the maintenance of vital bodily processes such as respiration, circulation, and biochemical reactions involved in the maintenance of the metabolism[1].

Indirect calorimetry (IC) is a noninvasive method for determining energy needs from the gas exchanges that takes place between the body and the environment, namely, the volume of oxygen consumed (VO_2), a major component of BEE, and the volume of carbon dioxide produced (VCO_2). This is obtained by analysis of air inhaled and exhaled by the lungs[2-3].

Prediction equations are used to establish a standard that will serve as a benchmark for the comparison of BEE in sick individuals. The Harris-Benedict Equation (HBE) is the most commonly used method to calculate BEE in clinical practice[4].

Measurement of BEE in healthy individuals, and also for different groups of diseases is essential for proper planning of nutritional therapy[5], with the purpose of avoiding the detrimental effects caused by both over and under eating[6].

The objective of this study was to determine by IC the BEE of patients diagnosed with squamous cell carcinoma of the esophagus (SCC) and to compare these findings with other parameters that make up a nutritional assessment.

Methods

Patients

The population studied consisted of 30 adult patients with a diagnosis confirmed by pathological examination of SCC, attending the group of gastrointestinal surgery, Hospital de Clinicas, Porto Alegre, from April 2009 until June 2011. The exclusion criteria were: patients previously treated with chemotherapy and/or radiotherapy and/or surgery, hypo/hyperthyroidism, chronic renal failure, diabetes mellitus, or patients with Human Immunodeficiency Virus (HIV). These criteria sought to exclude any clinical condition that might interfere with energy expenditure. The study was approved by the Research Ethics Committee of our institution and all participants signed a consent form.

Patients underwent a nutritional assessment upon admission in order to determine their nutritional status. The following measurements were recorded: body weight, height, body mass index (BMI) and percentage weight loss. Venous blood was sampled for levels of: albumin by bromocresol green colorimetry (reference value: greater than 3.5 g/dL); transferrin by immunoturbidimetry (reference values: 200 and 400mg/dL); C-reactive protein (CRP) by turbidimetry (reference values: up to 5.0 mg/L). The ADVIA® 1800 chemistry analyzer (Siemens, Japan) was used. Clinical staging of the disease was determined by the TNM classification of malignant tumors[7-8]. Patient lung capacity was also determined through spirometry and using the Tiffeneau Index (reference value: 60% or more of the expected value).

Body Composition

Fat free mass (FFM) was ascertained by means of bioelectrical impedance analysis using a body composition analyzer (model Bodystat® 1500). Participants were instructed to fast for 8 hours prior to the procedure, and in addition, to take no part in physical activity from the day before the exam until the procedure was completed[9].

Basal Energy Expenditure

BEE was measured in a thermoneutral environment by indirect calorimetry (CORTEX Biophysik MetaLyzer® 3B, Germany), after a fasting period of at least 6 hours. Patients were at rest for 30 minutes before data collection commenced. The system was calibrated in accordance with the instruction manual before each measurement. Oxygen consumption and carbon dioxide production were measured with the patient being in a supine position over a period of 25 minutes (including the initial time of 5 minutes). Measurement of the Basal Metabolic Rate (kcal/min) was obtained through the Weir equation[10]:

$$\text{Kcal/min} = \{[3.9(VO_2)] + [1.1(VCO_2)]\}$$

The equation as described by Weir (10) uses the last 20 minutes, after having first observed an initial 5 minute resting steady state, with the mean being multiplied by 1.440 to obtain the BEE for 24 hours.

Prediction Equation

The expected BEE was estimated using the Harris-Benedict Equation (HBE)[11]:

Women: BEE: 655+(9.6xW)+(1.8xH)-(4.7xA)

Men: BEE: 66.5+(13.8xW)+(5xH)-(6.8xA)

Where W represents weight, H is height, and A is age.

An additional method for prediction was included based on recommendations for the use of an injury factor for cancer of 1.3 in combination with the HBE[12].

Patients with a measured BEE of less than 90% of the predicted value were classified as hypometabolic, those between 90 and 110% as being normal metabolic, and those in excess of 110% as being hypermetabolic, as conforming with Boothby et al[13].

Statistical Analysis

Data analysis was performed using SPSS software (Statistical Package for the Social Sciences) version 18.0.

Quantitative variables were described through mean and standard deviation, except for measurement of CRP for which the median and range of variation were used. Categorical variables were described using absolute and relative frequencies.

Student's t-test for independent samples was used to compare continuous variables according to group.

Energy expenditure measured by IC was compared to values gained through estimation methods using Student's t-test for paired samples. When adjusted for FFM the analysis of covariance was applied. The Bland-Altman method was used for assessing agreement between the findings.

Pearson's chi-square test was applied to assess associations between categorical variables, and Pearson's correlation analysis when assessing associations between continuous variables.

The multiple linear regression model with backward elimination was used to control confounding factors. The criterion for entering a variable in the model was that it presented a $p<0.10$ in the bivariate analysis.

The Cochran test was used to compare methods of nutritional assessment. In the case of statistical significance, the McNemar test was applied to locate the difference.

The level of statistical significance considered was 5% ($p \leq 0.05$).

Results

Thirty patients with SCC were studied, this being 21 men (70%) and 9 women (30%) with an average age of 61.4 (± 8.6) years.

In relation to BMI, 8 patients (26.7%) were malnourished, 14 (46.7%) were of a normal weight and 8 (26.7%) were overweight.

Twenty-seven individuals (90%) lost weight and of these, 25 (83%) had a significant weight loss, resulting in a mean percentage weight loss of 13.2% (± 8.8). Anorexia was reported by 7 (23.3%) patients.

The percentage of FFM (%FFM) among individuals was 69.6% (± 7.7) and body fat 30.4% (± 7.7). Dysphagia related to solid and soft foods was present in 23 (85.2%) patients and in four (14.8%) patients for liquids. Patient characteristics are described in table I.

The mean for BEE measured by IC was 1421.8 (± 348.2) kcal/day; estimated by HBE was 1310.6 (± 215.1) kcal/day ($p=0.014$); estimated by HBE with inclusion of injury factor of 1.3 for cancer was 1703.8 (± 279.7) kcal/day ($p<0.001$).

Figure 1 demonstrates the association between %FFM and BEE measured by IC. It can be seen that the higher the %FFM, the higher the BEE.

Table II shows the mean differences, limits of agreement, and the population proportion that is included in the acceptable limits of ± 10%.

According to the classification of Boothby et al[13]., 6 (20%) patients were considered hypometabolic, 7 (23.3%) normal metabolic, and 17 (56.7%) hypermetabolic.

Nutritional status determined by BMI and % weight loss was linked with BEE measured by IC. A significant difference was found in the BEE between malnourished (1181.7 ± 278.1 kcal/day) and well nourished patients (1509.1 ± 334.1 kcal/day) by BMI ($p=0.020$), whereas no significant differences were found using % weight loss, 1403.4 ± 369.0 kcal/day and 1514.0 ± 222.0 kcal/day respectively ($p = 0.526$). The BEE for patients with a lower than expected %FFM was 1408.9 ± 364.3 kcal/day, as compared to 1538.4 ± 97.5 kcal/day for patients with an adequate %FFM ($p=0.550$).

Associations between BEE and demographic and-clinical characteristics of patients are shown in table

Table I
Demographic & Antropometric Characteristics of study (n =30)

Variables	*Value (%)*
Gender - n (%)	
Male	21 (70%)
Female	9 (30%)
Age (years) - Mean ± SD	61.4 ± 8.6
Weight (kg) - Mean ± SD	60.9 ± 13.6
Height (m) - Mean ± SD	1.65 ± 0.10
BMI (kg/m²) - Mean ± SD	22.4 ± 4.2
% FFM – Mean ± SD	69.6 ± 7.7
Staging - n (%)	
I	1 (3.3)
II	10 (33.3)
III	12 (40.0)
IV	7 (23.3)
Dysphagia - n (%)	27 (90.0)
Diet - n (%)	
Oral	10 (33.3)
NFT*	4 (13.3)
Oral+NFT	16 (53.3)
Weight Loss (%) - Mean ± SD	13.2 ± 8.8

*Nasoenteral Feeding Tube.

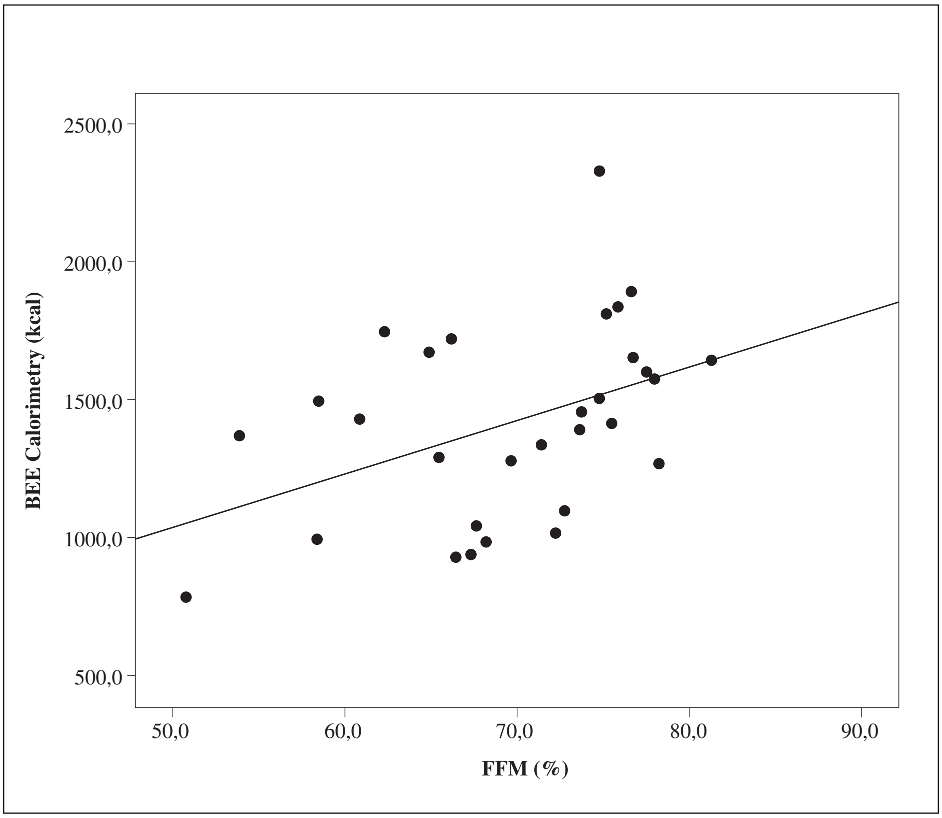

Fig. 1.—Association between BEE Calorimetry and FFM.

III. No association with BEE measured by IC was found between age (p=0.267), clinical staging (p=0.255) and the Tiffeneau Index (p=0.946). There was a significant association of BEE measured by IC with BMI (p=0.001) and %FFM (p=0.019).

No significant associations were found between BEE measured by IC and the pathology tests. In relation to transferrin in malnourished patients the BEE was 1504.9 ± 273.1 kcal/day and 1380.3 ± 379.8 kcal/day for the others (p=0.364); for albumin the figures were 1667.7 ± 119.2 kcal/day and 1404.3 ± 353.4 kcal/day respectively (p=0.309). In relation to CRP in patients with altered values the BEE measured by IC was 1403.6 ± 296.8 kcal/day and 1440.1 ± 402.8 kcal/day for the others (p=0.780). The mean for albumin was 4.1 ± 0.39 g/dL and for transferrin 218.1 ± 34.9 mg/dL. The median for the 16 patients who presented alterations in CRP was 10.2 mg/L (6.6 mg/L to 123 mg/L).

A multiple linear regression analysis was performed to evaluate independent factors associated with BEE measured by IC. The variables %FFM (p=0.002) and BMI (p<0.001) showed that the two factors together contributed 52.9% to BEE.

Discussion

Many studies in recent decades have investigated energy expenditure in cancer patients with some maintaining the idea that these patients have a high BEE which significantly contributes to the development of malnutrition[14], while others have found no change[15].

Our study found the mean BEE measured by IC of patients with SCC to be 1421.8 ± 348.2 kcal/day. Research by Reeves[16], which looked at post-radiotherapy patients with lung and gastrointestinal tract cancers found the mean BEE measured by IC to be 1589.4 ± 89.7 kcal/day. A further study by Thomson[17] involving only black patients with esophageal cancer found the mean BEE measured by IC was 1484.6 ± 200.7 kcal/day.

Table II
Predicted BEE, mean of differences, and limits and agreement for the differences between the predicted and measured BEE of patients with SCC

Variable	*Predicted value Mean ± SD*	*Difference Mean ± SD*	*Limits of agreement*	*Proportion within ± 10%*
HBE	1310.6 ± 215.1	-111 ± 234	-45.1 to 27	26.7%
HBE x 1.3	1703.8 ± 279.7	282 ± 230	-4.6 to 88.6	26.7%

Table III
Evaluation of association of BEE by Indirect Calorimetry with clinical characteristica

Variable	*BEE Calorimetry Mean ± SD*	*p-value*
Age (years) - R	-0.209	0.267
BMI (kg/m^2) - r	0.562	0.001
%FFM - r	0.427	0.019
Staging		0.255*
I/II	15212 ± 386.6	
III/IV	1365.2 ± 329.5	
TI (%) - r	-0.016	0.946

TI: Tiffeneau Index (FEV1/FVC); r = Pearson's correlation coefficient, *Student's t-test for independent samples.

In this study BEE was underestimated by the HBE by 111.2 kcal/day or 7.82%. The HBE was developed to evaluate the basal metabolism in healthy people, but can overestimate BEE by 5 to 15%[18], and underestimate BEE in malnourished patients[19]. In a study by Knox[20] which evaluated malnourished patients with cancer (gastrointestinal and gynecological), the BEE estimated by the HBE showed no statistically significant differences when compared to the BEE as measured by IC. The difference we found of 7.82% was statistically significant but cannot be considered clinically significant, as this would happen when there was a greater or lesser difference of at least 10%[11].

In order to improve the estimate of BEE by the HBE, studies have added an injury factor[21]. In this study the HBE with an injury factor of 1.3 overestimated the BEE by 282.4 kcal/day or 19.83%. In the study by Reeves (16), the BEE calculated by the HBE with injury factor overestimated by 373.7 kcal/day or 23.51%.

In relation to the acceptable clinical limits of agreement in terms of HBE and also HBE x 1.3, our research showed 26.7% and 26.7% of agreement, respectively. In the study by Johnson[22] using the HBE with a correction factor of 1.11, an agreement of 55.6% was obtained, whilst Reeves[16] describes an agreement of 50% by HBE, and 18.8% by HBE with injury factor of 1.3.

When considering Boothby's[13] equation, the result of our study found 20% of patients hypometabolic, 23.3% normometabolic, and 56.7% hypermetabolic. Other research by Cao[23] involving recently diagnosed cancer patients (esophagus, stomach, colorectal and pancreatic) produced results of 7.4%, 43.3% and 49.3%, whilst results for Dempsey[24] with malnourished gastrointestinal cancer patients were 36%, 42% and 22% respectively.

Associations were observed between BMI and BEE measured by IC. When evaluating women after 12 weeks on a calorie restricted diet, Kendrick[25] also found an association between BEE and BMI (r=0.68). Body size as defined by height and weight is an important determinant of BEE, although it is difficult to separate the specific effect of each factor[26,27].

Also observed was an association between the reduction in the %FFM and the decrease in BEE. According to Wilson and Morley[28], FFM is the primary determinant of BEE. Weight loss in patients initially occurs as a fat loss with this resulting in an observed increase in FFM. In situations where the %FFM increases, an equation based on weight will underestimate the BEE. Any such underestimation could be of clinical importance as underestimating the energy needs of a patient could impact on the effect of the nutritional therapy[29,30]. The study by Cao[23] demonstrated that cancer patients lose body fat more rapidly than FFM, which could be a possible mechanism for the increase in BEE as FFM is more metabolically active than fat.

The role of CRP as a predictor of survival has been demonstrated for different tumor types[31]. Our study showed no difference in the BEE of patients with altered CRP, albumin and transferrin readings. In the study by Johnson[22], CRP was increased in cancer patients who had had a significant weight loss and suffered from cancer cachexia syndrome, with the BEE for these patients also showing increases. The reason for this discrepancy with our results may be that the patients evaluated by Johnson[22] had cancer cachexia syndrome, which could mean that other factors may have influenced the increase in BEE, whereas in our study the cause of significant weight loss for the majority of patients was due to the obstructive nature (dysphagia) of the tumor, and not cancer cachexia syndrome. In patients with cancer the acute phase proteins may contribute to an increased BEE[32], which can promote weight loss[31].

In relation to lung capacity, there was no difference between the BEE in patients with a lower IF. The IF is used as an index sensitive to mild airway obstruction[33].

It should be noted that it was not possible to evaluate the IF of 4 patients, and of the others, only 4 had an altered IF. Nonetheless, there was a minimal reduction in BEE measured by IC in patients with IF alterations of 1.26%. No study to date has linked IF with BEE.

When considering BEE and the clinical stage of the disease, our study showed no significant difference in BEE between patients diagnosed at stages I and II and those at stage III and IV, with the latter groups showing a reduction in BEE of 10.29%. Dempsey et al[24]. have suggested that some cancer patients may in fact have a reduction in BEE, though Cao[23] concluded that the BEE of patients with stage IV cancer was higher than for stages I, II and III, and that type of cancer, stage and the time of diagnosis are responsible for the BEE, which is in agreement with some previous studies[34].

Conclusion

In conclusion, when comparing the BEE measured by IC of patients with SCC, it was found that the HBE with no injury factor underestimated BEE whereas the

HBE with injury factor of 1.3 overestimated the figure. The factors that contributed most to the increase of BEE measured by IC were BMI and FFM. The use of IC should always be considered since it is the «gold standard» method for determining BEE. However, even today the use of IC is not routine and thus further studies involving larger numbers of patients with SCC are necessary in order to identify the ideal injury factor to be used with the HBE, for those occasions when IC is not available.

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