■ ARTYKUŁ ORYGINALNY / ORIGINAL ARTICLE

Indirect calorimetry, indications, interpretation, and clinical application

Kalorymetria pośrednia, wskazania, interpretacja i zastosowanie

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ABSTRACT

The aim of this review is to inform clinicians about the new possibilities in clinical nutrition (enteral or parenteral) based on indirect calorimetry. This method allows for the provision of an appropriate number of calories to undernourished hospitalized patients for nutritional repletion or maintenance. Providing too few or too many calories may result in adverse clinical consequences and worsen the course of the disease, especially in critically ill patients. Thus, optimizing nutrition support according to the individual and specific needs of patients is an urgent task. Indirect calorimetry (IC) is the only practical, clinical method to measure resting energy expenditure (REE). However, from a clinical perspective, knowledge of only one part of total energy expenditure (TEE) is insufficient to plan feeding that covers the actual energy needs of an individual patient. Currently, there is no method better than IC for accurately determining the resting energy needs of hospitalized patients. Although many predictive equations for REE have been developed, none of them can account for all the factors associated with changes in metabolism in critically ill patients. The most widely used equation for this purpose, the Harris and Benedict equation, was issued over 100 years ago and is inaccurate in about 40% of patients. To date, indirect calorimetry remains the gold standard for assessing REE. This paper addresses how to use and interpret indirect calorimetry in planning clinical nutrition for critically ill patients.

Key words: indirect calorimetry, critically ill, indications, interpretation

STRESZCZENIE

Celem niniejszego przeglądu jest przedstawienie klinicystom nowych możliwości żywienia klinicznego (dojelitowego lub pozajelitowego) opartego na kalorymetrii pośredniej, która umożliwia dostarczanie odpowiedniej liczby kalorii w celu uzupełnienia składników odżywczych lub utrzymania niedożywionych pacjentów hospitalizowanych. Podanie zbyt małej lub zbyt dużej ilości kalorii może skutkować niekorzystnymi następstwami klinicznymi, pogorszyć przebieg choroby, zwłaszcza u pacjentów w stanie krytycznym. Dlatego pilnym zadaniem jest optymalizacja wsparcia żywieniowego dla indywidualnych i specyficznych potrzeb pacjentów. Kalorymetria pośrednia (IC, *indirect calorimetry*) jest jedyną praktyczną, kliniczną metodą pomiaru spoczynkowego wydatku energetycznego (REE, *resting energy expenditure*), ale z klinicznego punktu widzenia znajomość tylko jednej części całkowitego wydatku energetycznego (TEE, *total energy expenditure*) nie wystarcza do zaplanowania żywienia obejmującego rzeczywiste zapotrzebowanie energetyczne indywidualnego pacjenta. Obecnie nie mamy nic lepszego niż IC do dokładnego określania spoczynkowych potrzeb energetycznych hospitalizowanych pacjentów. Chociaż opracowano wiele równań prognostycznych dla REE, żadne z nich nie może wyjaśnić wszystkich czynników związanych ze zmianami metabolizmu u pacjentów w stanie krytycznym. Najczęściej używane równanie Harrisa i Benedicta, wydane ponad 100 lat temu, jest niedokładne u około 40% pacjentów. Do tej pory kalorymetria pośrednia pozostaje złotym standardem oceny REE. Jak ją wykorzystać i zinterpretować w planowaniu żywienia klinicznego u pacjentów w stanie krytycznym, jest tematem tego artykułu.

Słowa kluczowe: kalorymetria pośrednia, krytycznie chorzy, wskazania, interpretacja

INTRODUCTION

Total energy expenditure (TEE) in healthy individuals mainly consists of resting energy expenditure (REE), which represents 60-75% of TEE, activity expenditure (AE) — approximately 30% of TEE, and diet-induced energy expenditure (DEE) — about 10% of TEE. REE is mainly a product of the metabolism of lean body mass, and it is the smallest amount of energy that should be given daily to prevent the utilization of one's own energy sources, which leads to disease-related undernutrition [1]. Supporting appropriate amounts of energy is of paramount importance to optimize nutrition therapy for critically ill patients, as well as other severely undernourished patients with various pathologies and conditions. Since Harris and Benedict published their equation in 1919 [2], more than 200 predictive equations based on anthropometric data for measuring REE have been developed, but all have unacceptable high error rates. This error rate is magnified by the application of activity and injury factors to empirically account for total energy needs in critically ill patients [3]. Lean body mass is the strongest determinant of IC-measured REE, but the final result of measurement depends on many variables, such as body weight, height, sex, age, nutritional status, injury, infection, proper execution, and interpretation of obtained results. Critical illness can alter glucose metabolism (hyperglycemia), lipid metabolism (increased mobilization of free fatty acids), protein and amino acid metabolism (significant increase in protein breakdown), leading to significant increases or decreases in energy expenditure. Thus, exact knowledge of REE is crucial in patients receiving nutritional support to avoid complications associated with under- or overfeeding [4]. Underfeeding (undernutrition) resulting from inadequate intake, digestion, or absorption of protein and/or energy (calories) is an independent factor that increases morbidity, mortality, hospital stay, and treatment costs. Overnutrition results in overweight and obesity, both of which are associated with complications, including hypertension, heart disease, type 2 diabetes, non-alcoholic fatty liver, stroke, respiratory disorders, and cancer.

The measured REE obtained from IC is the best guide for energy administration during nutritional support. However, this method is only available in a small number of hospitals, mainly due to the high cost of the device and trained personnel who can perform the examination and interpret the results accurately. In 2000, the cost of indirect calorimetry was between 30 and 60 thousand dollars [5], and currently, there is no country that reimburses the cost of this examination. This is probably why Heyland et al. [6] showed in a 2011 paper that out of 8,500 critically ill patients treated in intensive care units worldwide, only 2% had their REE diagnosed based on IC, with the remaining 98% diagnosed using predictive equations, mainly Harris and Benedict, Ireton Jones, and Penn State equations. Four years later, Heyland et al. [7] showed that out of 3,390 critically ill patients treated in ICU-s in 26 European countries, only 2% had their REE measured using IC [7]. The main goal of this review is to examine how to interpret the results of indirect calorimetry in healthy and severely ill subjects and how to utilize the obtained results in malnourished (undernourished and obese) patients when planning clinical nutrition.

ENERGY EXPENDITURE

The energy required by the human body to maintain its organic and vital functions is obtained through the oxidation of macronutrients from food. Energy expenditure (EE) is the result of the combustion of carbohydrates, lipids, and proteins, which requires oxygen consumption and results in the production of carbon dioxide. Total energy expenditure (TEE) is the amount of energy required by the organism daily and is determined by the sum of three components: resting energy expenditure (REE), diet-induced thermogenesis (DIT), and physical activity (PA).

Resting energy expenditure (REE) is the amount of energy required to perform essential body functions, such as respiration, cardiac function, and maintenance of body temperature. REE is determined at rest, in a supine position, after 8 hours of sleep and a 12–14 hour overnight fast. REE contributes to 60–75% of TEE for most sedentary individuals and approximately 50% for physically active individuals. The strongest determinant of REE is lean body mass (LBM), but other factors such as sex, age, systemic inflammation, thyroid function, body temperature, body weight, and disease processes also influence REE. Clinical and surgical diseases usually increase REE by 5–20%. Fever is another important factor that increases REE by 11% for every 1°C. Conversely, medications such as sedatives, pain relievers, and muscle relaxants used to reduce metabolic stress seem to reduce REE.

Diet-induced thermogenesis (DIT) is the component of EE related to the energy required for the digestion, absorption, usage, and storage of nutrients after food intake. The thermic effect of food on TEE depends on the type and amount of nutrients and represents 5–15% of TEE. In patients on parenteral nutrition may be neglected, while in patients on enteral nutrition with oral nutritional supplements, it does not seem to exceed 5%.

Physical activity (PA) represents the thermic effect of any movement that exceeds REE. In sedentary individuals, it can represent less than half of the REE [8, 9, 10]. Energy needs can be assessed by indirect calorimetry or through the use of predictive equations or normograms proposed by scientific societies.

INDIRECT CALORIMETRY

Adapting nutrient supply to the actual requirements of critically ill patients is an essential part of their complex treatment, as both overfeeding and underfeeding can contribute to increased morbidity and mortality. Indirect calorimetry measures the oxygen (VO_2) consumption and carbon dioxide (VCO_2) excretion, allowing for the calculation of energy expenditure (EE) and respiratory quotient (RQ). According to the original Weir equation [11], the metabolic rate in calories per day can be calculated as *metabolic rate* [cal/day] = 1440 x (3,94 x + 1,11 x), where is the oxygen consumption in liters per minute and is the rate of carbon dioxide production in liters per minute. The formula can also be written in terms of calories per day, with expressed in milliliters per minute and expressed in milliliters per minute.

RESPIRATORY QUOTIENT RQ

The respiratory quotient (RQ) is used to evaluate substrate utilization and has a normal physiologic range of 0.7 to 1.0. Higher RQ values may indicate excessive CO_2 production, lipogenesis, and overfeeding, while values less than 0.7 may be due to metabolic or technical causes. However, obtained RQ values should be interpreted with caution as they can be altered by diseases, changes in acid-base balance, medications, and overfeeding. If the RQ is greater than 1.0, the total calories and/or carbohydrates should be decreased, while if the RQ is less than 0.7, the total calories should be increased. Since 2003, new IC devices that measure only VO_2 consumption have become available for clinical application in addition to calorimeters measuring both VO_2 and VCO_2. These devices are cheaper and more compact, and as hand-held units, can be easily carried from one subject to another. They provide a VO_2 value and resting energy expenditure (REE) on their liquid crystal window display, but since they only measure VO_2, it is not possible to determine RQ [12]. These highly portable devices are still in use mainly due to their lower price and easy service. However, no validation has been published in critically ill patients requiring mechanical ventilation because these devices cannot be used in this group of patients, significantly limiting their wide application.

INDICATIONS FOR INDIRECT CALORIMETRY

Indirect calorimetry is indicated in all clinical situations in which precisely measured energy expenditure is important to avoid under- or overnutrition, and to plan clinical nutrition based on actual energy needs. This method is particularly useful for the following groups of patients:

- Critically ill patients treated in the ICU.
- Oncological patients with severe undernutrition or cachexia, in whom clinical nutrition adjusted to requirements is an important part of treatment.
- Patients with severe acute pancreatitis or acute necrotic pancreatitis, who quickly develop mixed undernutrition or acute kwashiorkor undernutrition, and in whom early enteral or parenteral nutrition is widely accepted as a complex treatment in these cases.
- Patients after severe multi-organ or cranio-cerebral trauma, in whom energy expenditure increases by up to 40%.
- Severely obese patients before and after bariatric surgery, in whom IC is useful in planning a proper diet. This should be complemented by body impedance analysis (BIA) to determine whether loss of body weight is primarily due to loss of fat mass or lean body mass, which is undesirable and leads to undernutrition [13, 14].
- Patients suffering from Coronavirus Disease 19 SARS (COVID-19) with severe acute respiratory syndrome, immunodeficiency, and undernutrition should be fed enterally as soon as possible with oral nutritional supplements (ONS) according to their energy needs. If possible, these needs should be measured by indirect calorimetry, to allow adjustment of the amount of macronutrients based on their actual energy requirements [15].

INDIRECT CALORIMETRY MEASUREMENT

The first step in obtaining high-quality results from indirect calorimetry is to evaluate the patient's preparation for the test. Because energy expenditure is significantly affected by the intake of nutrients, nicotine, caffeine, alcohol, duration of rest, and restraint of physical activity prior to testing, all these factors must be carefully evaluated before starting the measurement. Prior to testing, the patient should:

- Be fasting for a minimum of 5 hours after meals or snacks.
- Abstain from alcohol and nicotine for at least 2 hours and from caffeine for 4 hours.
- Abstain from moderate exercise for at least 2 hours and from vigorous exercise for up to 14 hours.
- Inform the person performing the examination about all medications taken daily.
- The patient should receive these recommendations no later than 2 days before testing.

Patients on ventilators in a critical care unit have frequent interventions, such as sedation and nursing care procedures, which can alter energy expenditure and should be taken into consideration. Indirect calorimetry measurement should be performed at room temperature (20–25^{0}C) because in this range of temperatures, the energy expenditure necessary to keep the body's temperature stable is smallest [16–18]. The acceptable length of the test is still a point of discussion. The most common protocol in the critical care area is a 30-minute collection of data. In other patients, a measurement lasting 20 to 30 minutes seems to be sufficient to calculate total energy expenditure. The optimal length of rest prior to measuring REE is also a matter of discussion, but according to most investigators, 10 to

20 minutes is recommended [16, 17]. Achieving a steady state during IC testing is recommended to assure validity and reduce error from artifactual influences. Unfortunately, the need to achieve a steady state during IC testing is controversial. This controversy is reflected in a lack of consensus on the methodology for performing IC testing. The actual criteria for a steady state are variably defined as a 5-minute interval during which either average minute VO_2 and VCO_2 change by <10%, VO_2 and VCO_2 vary about their mean values by ≥ 5%, or the coefficient of variation of both VO_2 and VCO_2 is ≤ 5%. Other investigators provide more clinically oriented criteria for a steady state defined as „the patient is lying motionless with eyes open and responding to surrounding events" [16, 17].

According to Clave et al. [19], failure to achieve a steady state does not invalidate the results of the study but signifies greater error in extrapolating the short-term REE to the 24-hour TEE.

FACTORS INFLUENCING ENERGY EXPENDITURE

Age: Age-related changes in body composition and cellular energy metabolism influence subcomponents of total energy expenditure (TEE). The decrease in resting energy expenditure (REE) is mainly related to the progressive increase of less metabolically active fat mass (FM) and the decrease of metabolically active fat-free mass (FFM), as well as a reduction in organ mass that progresses with age. These changes significantly diminish the value of prediction equations in older subjects and may lead to inadequate nutritional interventions in this still-increasing group of hospitalized patients. Other causes that lead to diminished energy expenditure in older subjects include a progressive lack of appetite, reduced physical activity, and chronic diseases, which are responsible for a progressing decrease in REE starting from the age of 30. Although 20 kcal/kg body mass has been suggested for predicting energy expenditure in elderly ICU patients, the measurement of REE by indirect calorimetry is still recommended for an accurate assessment of individual resting energy needs in this group of patients [1, 8, 18, 20, 21].

Gender: REE in women is always lower, by 100–200 kcal/24 h, than in men of the same weight, height, and clinical condition due to a physiologically higher amount of less metabolically active fat mass in a woman's body.

Obesity: Another unsolved problem is planning nutrition adapted to requirements, which is extremely difficult in cases of obesity. Obesity is one of the most common chronic diseases in the United States and is growing at a disproportionate rate worldwide, which means that the number of obese critically ill patients in hospitals will also be increasing every year. Before starting effective treatment for an obese patient, it is necessary to exclude the most common comorbidities such as cardiovascular diseases, type 2 diabetes, gastrointestinal symptoms, musculoskeletal disorders, respiratory problems, and some cancers. Identifying these comorbidities is of great importance because they play a significant role in the metabolism of obese patients. Obese ICU patients are catabolic, and in the postoperative period, their total resting energy expenditure is higher than that of lean patients but may be lower per kg body weight. The appropriate amount of calories and protein to be given to obese ICU patients is still a matter of ongoing debate.

When comparing hypocaloric diet (<15 kcal/kg current body weight (CBW) per day) to normocaloric diet (25–36 kcal/kg ideal body weight (IBW) per day) with high protein intake (1.8–2.2 g/kg IBW per day), the former showed slight advantages, such as lower insulin requirements, better wound healing, decreased ICU stay, and antibiotic days [19, 20]. Hypocaloric feeding may begin at 50–70% of the estimated caloric requirement (or 11–14 kcal/kg CBW, or 22–25 kcal/kg IBW), while high protein feeding may begin from 1.2 g/kg CBW or 2.0–2.5 g/kg IBW. It is important to note that providing hypocaloric, low protein feeding is associated with a poor clinical outcome and should be avoided in clinical practice [19]. In patients without severe renal or hepatic dysfunction, adequate protein provision and enteral route of feeding are highly recommended [19, 20, 21].

It should also be remembered that in obese patients, micronutrient deficiencies occur more frequently than in the general population. Vitamin deficits mainly concern vitamin D, A, and folic acid. Additionally, minerals such as iron, calcium, iodine, magnesium, zinc, and selenium were found at lower levels in obese compared to lean individuals [8, 19, 20]. Obese patients in the ICU are usually highly catabolic and should be fed early to minimize loss of lean body mass. Energy requirements are best determined by indirect calorimetry since predictive equations are inaccurate, especially in this group of patients [22–24].

WHICH WEIGHT SHOULD BE USED IN PLANNING CLINICAL NUTRITION

Loss of body weight is commonly associated with inadequate nutrition, and weight loss greater than 10% of usual body weight suggests severe undernutrition. However, in critically ill patients, weight loss can be masked by edema and does not reflect true body mass. Unfortunately, there is still no consensus from ASPEN and/or ESPEN on which body weight should be used in planning clinical nutrition. The following options are available:

Current body weight based on Body Mass Index (BMI) [25], which allows for the subdivision of measured weight into undernutrition (below 18.5 kg/m^2), normal body weight (18.5–24.9 kg/m^2), excess weight (25–29.9 kg/m^2), obesity 1^0 (30–34.9 kg/m^2), obesity 2^0 (35–39.9 kg/m^2), and morbid obesity 3^0 (> 40 kg/m^2) [25].

Actual Body Weight, which is the weight measured during hospitalization without any additional information.

Ideal body weight, which is related to height according to the following equation: Males should allow 48 kg for the first 152 cm of height and 1.07 kg for every additional cm of height [26]. The original equation values are expressed in pounds, feet, and inches.

Desirable body weight, which can be calculated using BMI (18.5–24.9 kg/m^2) or Broca's formula. Broca's formula is useful for patients aged 18 to 60 years and is calculated as follows: for males, (height [cm] – 100) – 5%, and for females, (height [cm] – 100) – 10% (Paul Broca, French surgeon, 1824–1880).

Due to the lack of consensus, most authors describe the intake of energy or protein using the abbreviation kg/mc, without providing information about the basis of the planned intake of macro- and micronutrients and energy.

INTERPRETATION OF RESULTS OF INDIRECT CALORIMETRY

Total energy expenditure (TEE) refers to the amount of energy required by the body on a daily basis, and is comprised of three components: resting energy expenditure (REE), diet-induced thermogenesis (DIT), and physical activity (PA). REE, also known as basal metabolic rate (BMR), represents the number of calories expended per hour, which can be extrapolated to a 24-hour period. REE accounts for 60–70% of the daily TEE in healthy patients at rest. Measurement of REE must be performed under standardized ambient conditions, as recommended for both indirect calorimetry and predictive equations [27]. All components of metabolism are mainly dependent on the clinical condition of the patient. In healthy subjects, REE and the other components of TEE are strictly defined. However, critically ill patients treated in the ICU have a different metabolism, which can increase with the severity of disease, organ failure, infection, inflammation, fever, catabolism, or sepsis. In the literature, results of indirect calorimetry for severely or critically ill patients are often presented as resting energy expenditure, which is accurate for healthy individuals but not necessarily true for ICU patients [10,12]. This is because the metabolism of the human body cannot be separated from the clinical status of the patient. In 2004, Holdy [12] introduced the term Measured Resting Energy Expenditure (MREE) with IC to formulate a calorie prescription according to the clinical status (patient category) and wrote: „In mechanically ventilated patients in the ICU, the MRRE equates to TEE, without any additional correction factors." Seventeen years later, Oshima, Singer, Pichard et al [1] stated, "by definition, BEE as well as REE measurements must be conducted in conditions that are unfeasible for diseased individuals. In clinical practice, REE or TEE reflects the patient's energy needs. For patients in the ICU, measured energy expenditure should be considered as TEE." This important statement, published in 2017 and based on human metabolism physiology, did not arouse much interest among clinicians. Until now, the term REE is commonly used as a result of IC in critically ill patients treated in the ICU. Adopting this statement requires changes in the interpretation and practical use of indirect calorimetry in planning clinical nutrition for ICU patients. In these patients, the term REE should be replaced by total energy expenditure [TEE] or actual energy expenditure [AEE]. In healthy subjects, it should be REE, which accounts for about 70% of TEE, and to obtain TEE, the value of REE should be multiplied by 1.1, 1.2, or 1.3. This is confirmed by our own unpublished data in which the mean measured value of IC in 50 surgical patients without signs of malnutrition was 1,650 kcal in males and 1,520 kcal in females. In severely ill mechanically ventilated patients treated in the ICU due to severe COVID-19, the mean energy expenditure was 2,258 kcal/day [28]. In 2021, Rattanachaiwong and Singer [29], based on their own experience, published an important statement that should be taken into consideration by physicians working in the ICU: "To minimize energy debt in the intensive care unit, we support early enteral feeding. REE should be measured as soon as the patient's condition allows, and the target of delivered calories should be around 0.7 to 1 of the measured REE to avoid overfeeding."

We completely agree with all of the statements supported by Pierre Singer, the "guru" of indirect calorimetry. Based on the literature and the description of human metabolism formulated many years ago, we believe it is time to take the next step and leave the term REE for healthy subjects, in whom three parts of metabolism are clearly distinguished (TEE = REE + DIT + PA). Instead, we should accept the term total energy expenditure (TEE) or actual energy expenditure (AEE) for the results of correctly performed indirect calorimetry in severely ill ICU patients. Accepting the statement that in ICU patients measured REE = TEE sets the goal of nutrition support, but in the clinical setting, we still do not know how many calories should be given to each individual patient, if according to the literature, providing 60 to 70% of the goal is sufficient to maintain gut integrity, provide stress prophylaxis, and improve the effect of an immune-stimulating diet [30, 31]. Delivery of calories below actual requirements will result in inadequate nutritional repletion or maintenance and worsen clinical outcomes. The clinical consequences of excessive caloric supply are less clearly defined, but hepatic dysfunction is often suggested. In light of the clinical consequences of both inadequate and excessive caloric supply, and our inability to precisely identify energy expenditure by means of predictive equations, indirect calorimetry remains the most reliable method for determining energy expenditure. However, the interpretation of results should differ for healthy subjects and severely ill ICU patients, due to the completely different metabolic situations of these non-comparable population groups.

CONCLUSIONS

Malnutrition is associated with increased morbidity, mortality, prolonged hospital stays, and higher treatment costs. Nutritional treatment, including oral nutritive supplements and enteral or parenteral nutrition, improves outcomes, but determining the appropriate amount of energy and protein to avoid underfeeding or overfeeding is challenging. Predictive equations are inaccurate and unreliable for critically ill population, which is heterogeneous, and has continual metabolic changes. This increases the difficulty of finding one predictive equation, which would be accurate for various groups of patients. For the past 100 years, widely used Harris and Benedict equation is inaccurate in 39% of patients, but up to now nothing better has been discovered. For more than 50 years, indirect calorimetry (IC) has been the gold standard for assessing energy expenditure (EE) in healthy or severely ill patients treated in the ICU. However, the terminology used for describing IC results for resting energy expenditure (REE) is incorrect and does not consider the different metabolic statuses of healthy and severely ill patients. Thus, we strongly support the statement made by Oshima et al. [1], Holdy [12], and Ratltanchaiwong and Singer [27] that in critically ill patients, IC results represent total energy expenditure (TEE) and often require reducing the indicated calorie amount rather than using additional factors like 1.1, 1.2, 1.3, to obtain TEE from REE, which in healthy subjects only represents 60 to 75% of TEE. We suggest that, to improve communication and avoid interpretation mistakes, IC results in severely ill ICU patients should be named TEE or actual energy expenditure (AEE). The term REE should be reserved for healthy subjects or moderately malnourished patients whose metabolism is nearly normal.

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