Review Article

Indirect Calorimetry: From Bench to Bedside

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Abstract

Accurate determination of energy expenditure (EE) is vitally important yet often neglected in clinical practice. Indirect calorimetry (IC) provides one of the most sensitive, accurate, and noninvasive measurements of EE in an individual. Over the last couple of decades, this technique has been applied to clinical circumstances such as acute illness and parenteral nutrition. Beyond assessing the nutritional needs, it has also shed light on various aspects of nutrient assimilation, thermogenesis, the energetics of physical exercise, and the pathogenesis of obesity and diabetes. However, because of little or no experience with IC provided during medical education, the benefits of IC are poorly appreciated. Newer technology, cost-effectiveness, and a better understanding of how to interpret measurements should lead to more frequent use of IC. This review focuses on the physicochemical background of IC, the various indications for use, techniques and instruments, potential pitfalls in measurement, and the recent advances in technology that has adapted the technique to long-term studies in humans.

Keywords: Energy expenditure, indirect, calorimetry

Introduction

The ultimate goal of nutrient metabolism is the production of energy. The most common way of extracting the chemical energy of a substrate is to completely oxidize it to carbon dioxide (CO_2) and water (H_2O). The final common pathway of all cellular fuels, i.e., carbohydrates (CHOs), fats, and proteins, is thus oxidation. The heat generated by biologic combustions is utilized to maintain body temperature. However, the body cannot use heat to perform work because of isothermia. The chemical energy liberated by oxidation is in part lost as heat and in part trapped in a variety of high-energy compounds, the most important, of which is adenosine triphosphate. Chemical (biosyntheses), osmotic (active transports), and mechanical (muscular contraction) work are thus made possible. For all biochemical reactions *in vivo*, the fundamental principles of thermodynamics are equally relevant. Thus, while the first principle of thermodynamics states that energy can neither be created nor destroyed, but can only be exchanged between the body and its environment, the second principle elucidates that the change in the total energy content of a system results in a change in both the free energy and the entropy of the system.

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Energy Expenditure

The total energy expenditure (TEE) is defined as the amount of heat energy used by the human body for daily functioning[1] and can be divided into three main components [Figure 1]:

1. Basal energy expenditure (EE) or resting EE (REE): energy used to sustain vital functions at rest,
2. Diet-induced thermogenesis: energy used during substrate metabolism postprandial,
3. Activity EE: Energy used in physical activity.

By definition, REE[2] is the energy required to maintain the body's basic cellular metabolic activity and vital functions, such as respiration and body temperature, in the absence of recent food intake, physical activity, and psychological stress.

Principle of Indirect Calorimetry

Human energy stems from chemical energy, which is released from nutrients through the oxidation of food substrates.

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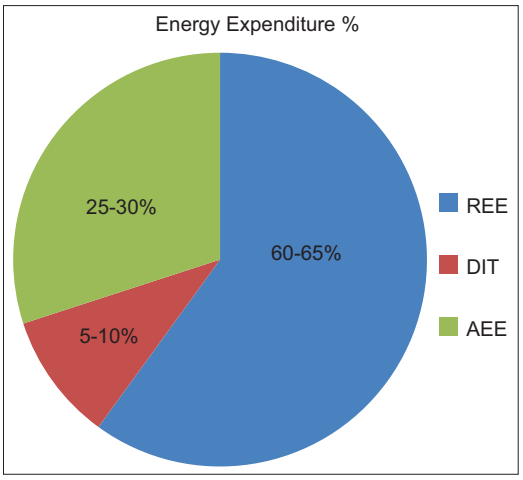

Figure 1: Components of total energy expenditure. REE: Resting energy expenditure, DIT: Diet-induced thermogenesis, AEE: Activity energy expenditure

Carbon-based nutrients (i.e. fuels) are converted into CO_2, H_2O and heat in the presence of oxygen (O_2). Indirect calorimetry (IC) assesses the amount of heat generated indirectly according to the amount and pattern of substrate used and byproducts generated. Specifically, EE can be calculated by measuring the amount of oxygen used (VO_2), and carbon dioxide released (VCO_2) by the body. The calculation of VO_2 and VCO_2 forms the inherent principle of IC. Total average daily EE in kcal is usually calculated using the modified Weir equation[3] as follows:

$$EE\ (kcal/day) = ([VO_2 \times 3.941] + [VCO_2 \times 1.11] + [uN_2 \times 2.17]) \times 1440$$

The urinary nitrogen component (uN_2) is often excluded when calculating EE because it only accounts for around 4% of the true EE. It contributes only to a small error of 1%–2% in the calculation of final EE in both inpatients and outpatients. Thus, the abbreviated equation is commonly used.[1]

$$EE\ (kcal/day) = ([VO_2 \times 3.941] + [VCO_2 \times 1.11]) \times 1440$$

Respiratory Exchange Ratio and Respiratory Quotient

The ratio of CO_2 produced to O_2 consumed is called the respiratory exchange ratio (RER) and is measured by the gases exchanged at the mouth. Since these values are measured at the mouth and not in the lungs, RER is the term utilized to represent fuel oxidation by IC. Similar measurements made at the cellular level, i.e. the ratio of CO_2 produced/O_2 consumed, is called the respiratory quotient (RQ).[4] The estimation of RQ, during steady state conditions, is integral to the calculation of EE by IC.

The RER is a useful indicator of the type of fuel (fat vs. CHO) that is being metabolized. During CHO metabolism, there is an equal amount of CO_2 produced for O_2 consumed (RER = 1.0). During fat metabolism, there is less CO_2 produced for O_2 consumed. Thus, depending on the substrate oxidized, the value of RER tends to vary. The physiological RQ tends to vary between 0.67 and 1.20. The RQ for lipids and proteins are approximately 0.69 and 0.82, respectively.[5]

Factors Influencing Respiratory Quotient and Respiratory Exchange Ratio

Although RQ and RER are the same measurement, under certain circumstances the values can differ as the components of the measure are obtained differently (cell respiration vs. exhaled air from the lung). The maximal range of RQ is from 0.7 to 1.0. The range of RER may vary from <0.7 to >1.2. Under steady state, the RQ and RER are equal. The RQ and RER may vary under following conditions: metabolic acidosis, nonsteady state exercise, hyperventilation, excess postexercise VO_2, prolonged exercise (if CHO nutrition was poor and muscle and liver glycogen are low, the longer the exercise session, the greater the amino acid oxidation).

Modalities of Measurement

There are a number of modalities of IC being used in practice. One of the earliest tools used is the Douglas bag which requires technical expertise and expensive analyzer equipment, apart from being prone to frequent air leaks.[6] The modern calorimeters are based on the multicomponent metabolic carts[7] that encompass the different devices such as a hood/mouthpiece [Figure 1], gas analyzers, and mixing chambers. Novel modalities involving heat flux sensors mounted on a small armband[8] are being used experimentally in the ambulatory setting for lifestyle modification such as weight management, fitness improvement, and diabetes care. However, long-term data validating these new techniques are lacking and use in critically ill patients needs to be carefully analyzed.

Prerequisites for Measurement

A number of studies have focused on the optimum conditions for carrying out an IC. Measurements must be conducted with strict adherence to resting conditions for accurate results.[9] Measurements should be performed in a quiet environment with the individual resting for 10–15 min before the measurement. The subject should be fasting for at least 5 h, avoid exercise for at least 4 h and avoid nicotine, caffeine, and stimulatory nutritional supplements for at least 4 h before the calorimetric assessment.

Validation of the Study

The validity of measurements on an indirect calorimeter is tested with respect to RQ and the steady-state period. A set of stringent criteria is followed to ensure accurate validation of the test.[10] The RQ within the physiologic range of 0.67–1.3 validates the IC measurements. The value of RQ measured, if found to lie outside the normal physiological range may have different connotations. The commonly encountered pitfalls in measurement of RQ[6] include air leaks in the respiratory

circuit, extreme pain or agitation during the measurement, or recent procedures that affect gas exchange (e.g., hemodialysis). Under or overfeeding can also affect RQ as can the proportion of CHO and fat in the diet. Approximately 5%–8% of ventilated or ambulatory patients tested with a "classic" metabolic cart have an RQ outside of the physiologic limit, thus invalidating the test. A valid test requires a "steady state" period of gas exchange defined by a 5-min interval during which VO_2 and VCO_2 vary by <10%.

McClave *et al*.[11] have determined that in mechanically ventilated patients, a 5-min steady state, defined by the most stringent criteria (VO_2, VCO_2 vary by <10%), best represents the measured 24-h TEE (R = 0.942–0.960). Reeves *et al*.[12] recently reported that a steady state as short as 3 min, especially in ambulatory patients or healthy volunteers, reflects a clinically acceptable REE. Steady state can generally be achieved within a test time of 30 min. However, it may have to be extended depending on the clinical scenario.

Determinants of Resting Energy Expenditure

A number of factors could either increase or decrease the measured REE (mREE) [Table 1] and hence could act as potential sources of error. These should be thoroughly evaluated before applying the REE data to any clinical setting. A number of studies have shown that fat-free lean mass most closely correlates with REE independent of age, body mass index (BMI), glycemic status, and other metabolic variables.[13] While REE is found to be higher in males,[14] fever, cold exposure, and hypothermia have also been implicated in causing an elevated REE.[15] Studies have further shown that 20%–30% of diseased states initially cause decline in REE due to release of catabolic counter-regulatory factors and drop in VO_2 preceding hemodynamic instability.[16] Subsequently, around 65%–75% of diseased states cause increase in REE. Interestingly, routine nursing procedures, such as a bed bath, dressing change or repositioning, even in comatose patients, have all been documented to increase EE by 20%–36%. The other important determinant of REE is concomitant drug usage.[17] Of these, agents such as caffeine, nicotine, and catecholamines can cause an increase in REE by 10%–20%. Decline in REE is usually associated with sedatives, analgesics, and alpha and beta blockers. The effect of thyroid hormone on EE in humans is significant; EE can decrease or increase up to three times compared to baseline in hypo- or hyperthyroidism.[18] A physiological dose of glucagon increased EE in humans during euinsulinemia while hyperinsulinemia blunted glucagon's thermogenic activity.[19]

Table 1: Factors affecting resting energy expenditure

Increased REE	Decreased REE
Cold exposure	Prolonged fasting
High altitude	Drugs: Sedatives, beta blockers, etc.
Exercise	
Pregnancy and lactation	
Ethnicity: Caucasians	
Hormones: Thyroid, glucagon	
Stress, Illnesses	

REE: Resting energy expenditure

Utility in Metabolic Studies in Diabetes and Obesity

Energy homeostasis is the balance between energy intake and EE. Assessment of energy intake is unreliable, especially in obese individuals. On the contrary, it is possible to assess EE by means of different techniques. It is in this aspect that IC has proved pivotal to the comprehension of the pathogenic mechanisms of obesity and diabetes mellitus. It has helped in developing knowledge regarding EE and its components, effects of dietetic manipulation of the relative fractions of macronutrients, and also genetic influences in obese people. IC has been useful in realizing that the alterations typical of insulin resistance are reproducible *in vivo* in healthy humans, increasing the availability of free fatty acids. In fact, IC has contributed to understanding the *in vivo* mechanisms of substrate competition, which was hypothesized more than 40 years ago. The postabsorptive assessment of REE and macronutrient partitioning in fuel metabolism may be helpful in designing long-term therapeutic strategies.

Predictive Equations in Metabolic Studies: A Viable Alternative?

Measuring REE as an approach to estimating total energy requirements has long been preferred to the use of dietary assessment methods because it is less time-consuming, simpler, and does not rely on the subjects' recall of food eaten, which often underestimates total energy needs.[20] Due to the limited access to equipment that measures REE, predictive equations such as Harris–Benedict (HB), Mifflin-St. Jeor, FAO/WHO/UNU, ICMR, Cunninghams, Owen, Mifflin, Katch-McArdle, Nelson to name a few, have been developed using readily available variables known to affect it such as gender, weight, height, or age.[21] Many of the published predictive equations used to estimate REE in obese persons have been developed from data collected in normal-weight individuals[22] or if they included persons of varying weights, did not report a separate analysis for the obese subsample.[23,24] It has been suggested that the equations may be inaccurate in participants with proportionately more adipose tissue.[25] Resting metabolic rates (RMRs) of adipose tissue are low (19 kJ/kg/day) compared with those for skeletal muscle (54 kJ/kg/day), liver (837 kJ/kg/day), brain (1004 kJ/kg/day), and heart and kidneys (1841 kJ/kg/day).[26] The most commonly used equations, published by Harris and Benedict in 1919, have been shown to overestimate basal energy requirements in healthy normal-weight persons up to 15% as compared with REE measured by IC.[27] Studies involving samples of normal-weight and obese persons combined have found an overestimation of 5%–13% by the Harris and Benedict equations.[28] Heshka *et al*.[29] cross-validated 12 published predictive equations with mREE

in a sample of 126 healthy obese persons and found that most overestimated REEs and that up to 40% of the variability in mREE remained unexplained by the variables used,[30] such as height, weight, and age. They also found that in equations using calculated body surface area in their formula, the size of the mean error was smaller.[31] Kross *et al*.[32] evaluated the accuracy of multiple regression equations to estimate REE in critically ill patients, especially for obese patients. A total of 927 patients were identified, including 401 obese patients. There was bias, and poor agreement between mREE and REE predicted by the HB, Owen, American College of Chest Physicians, and Mifflin equations ($P > 0.05$). In all cases, except Ireton-Jones (IJ), predictive equations underestimated mREE. The authors concluded that none of these equations accurately estimated REE in this group of mechanically ventilated patients, most underestimating energy needs. Ullah *et al*.[33] compared mREE using the IC with commonly used prediction equations, considering that the accuracy of prediction equations for estimating REE in morbidly obese patients is unclear. A total of 31 morbidly obese patients (46 kg/m^2) were studied. Preoperative REE with IC was measured and compared with estimated REE using the HB and Schofield equations. All patients subsequently underwent a Roux-en-Y gastric bypass and measurements were repeated at 6 weeks and 3 months following surgery. The HB and Schofield equations overestimated REE by 10% and 7%, respectively. After weight loss, the difference between the estimated and mREE reduced to 1.3%. The accuracy improved after surgery-induced weight loss, confirming their validity for the normal weight population. The study demonstrated that IC should be used in morbid obesity. Similar studies to validate the published predictive equations have been reported by Kim *et al*.[34] Alves *et al*.[35] compared the RMR obtained by IC with prediction equations (HB and IJ) in 44 patients with excess body weight. The nearest RMR in fasting was obtained with the HB equation using the current body weight (1.873 + 484 kcal/day and 1798 + 495 kcal/day for HB and IC, respectively). These studies emphasize the need to employ IC for the determination of EE in obese because despite the similarity found between the absolute REE measured by IC and the prediction equations, there are significant ranges of variability, suggesting that the ideal and more accurate method to obtain the actual REE in this population is the IC.

Application in Metabolic Studies

IC has formed the core of a number of metabolic studies that have looked at the pathogenesis of obesity, the influence of genetic polymorphism in metabolic diseases, and role of dietary interventions.

Genetic studies utilizing IC were conducted in sixty obese women (34.59 ± 7.56 years) to evaluate the influence of fatty diet and peroxisome proliferator-activated receptor γ2 (PPARγ2) and β2-adrenergic receptor genes on energy metabolism. It was found that polymorphism in PPARγ2 gene resulted in increase in fat oxidation, regardless of genotype of β2-adrenergic receptor gene.[36]

Polyunsaturated fatty acids (PUFAs) intake can assist in weight loss, but the genotype of the genes assessed determines the type of fat that should be ingested (the same research group developed another study with sixty obese women (30–46 years) which were divided into two groups depending on the genotype of PPARγ2 (Pro12Pro and Pro-12Ala/Ala12Ala). At baseline and after two nutritional (short- or long-term) interventions, it was observed that the Pro12Ala polymorphism in the PPARγ2 gene influenced energy metabolism in the assayed short- and long-term situations since the response to both nutritional interventions differed according to the genotype. The results suggest that fat oxidation and EE may be lower in Pro12Pro carriers compared to Pro12Ala/Ala12Ala genotypes, while in obese women with Pro12Ala/Ala12Ala polymorphisms in the PPARγ2 gene fat oxidation was negatively correlated with the monounsaturated fatty acids (MUFAs) and PUFA (%) intake.[37] The difference in the structure of fatty acids, including the chain length, degree of unsaturation, and the position of the double bond can affect the rate of oxidation of fatty acids. Using IC studies, it was indicated that the PUFA show higher oxidation compared to saturated fatty acid (SFA), both in men and in obese normal.[38,39] Piers *et al*.[40,41] found that changes in the type of dietary fat may have a beneficial effect on reducing body weight in men who consume high-fat content since the postprandial oxidation rate of nutrient (assessed by IC) is increased after a high MUFA meal compared with the SFA. Another case–control study was conducted to evaluate whether postprandial abnormalities of EE and/or lipid oxidation are present in healthy, normal-weight individuals with a strong family history of obesity and thus at high risk to become obese. Calorimetric data[42] showed that postprandial CHO oxidation (incremental area under curve) was significantly higher and that of fat oxidation lower in the group of individuals with overweight parents. They concluded that normal weight individuals with a strong family history of obesity present a reduced fat oxidation in the postprandial period. These metabolic characteristics may be considered the early predictors of weight gain and are probably genetically determined.[43] Differences in meal-induced thermogenesis and macronutrient oxidation between lean (n = 19) and obese (n = 22) women after the consumption of two different isocaloric meals, one rich in CHO and one rich in fat were studied based on REE and macronutrient oxidation rates in the fasting state and every hour for 3 h after meal consumption. Their results suggest that meal-induced thermogenesis and macronutrient oxidation rates were not significantly different between lean and obese women after consumption of a CHO-rich or a fat-rich meal.[44] IC has been used to look at the effects of a moderate-fat diet, high in MUFAs and a low-fat (LF) diet on EE and macronutrient oxidation before and after a 6-month controlled dietary intervention in 27 overweight (BMI 28.1 + 0.4 kg/m^2), nondiabetic individuals (18–36 years) followed over an 8-week period. These showed that despite a slightly lower meal-induced thermogenesis,[45] the MUFA diet had an effect on 24-h EE that was not significantly different from that of the LF diet after a 6-month controlled dietary intervention.[46] Indirect calorimetric

studies in 24 healthy, overweight men (BMI between 25 and 31 kg/m^2) have suggested that consumption of a diet rich in medium chain triglycerides (MCT) results in greater loss of adipose tissue compared with long chain triglycerides, perhaps due to increased EE and fat oxidation observed with MCT intake.[47] A controlled randomized dietary trial was conducted with 26 overweight or moderately obese men and women (BMI 28–33 kg/m^2) to test the hypothesis that n-3-PUFAs lower body weight and fat mass by reducing appetite and *ad libitum* food intake and/or by increasing EE. Their results suggest that dietary n-3-PUFA do not play an important role in the regulation of food intake, EE, or body weight in humans.[48,49]

Indirect Calorimetry: The Indian Perspective

A number of Indian studies have attempted to look at EE, body composition, and nutritional intake in various subgroups of the Indian population.[50]

Behera *et al*., in a novel study in patients with fibrocalculous pancreatic diabetes (FCPDs),[51] studied a total of 51 males in three groups comprising FCPD ($n = 24$), type 2 diabetes ($n = 15$), and healthy controls ($n = 12$). The body composition was measured using dual-energy X-ray absorptiometry, and the REE was estimated using IC. The predicted EE (PEE) was calculated using three different equations. Patients in both groups with diabetes had a higher mean waist-hip ratio than the controls ($P = 0.002$). However, patients with Type 2 diabetes alone had a significantly higher mean BMI ($P = 0.012$), percentage of fat ($P = 0.016$), and total fat content ($P = 0.031$). There was no significant difference in REE among the three groups. However, after adjustment of BMI, the REE was significantly higher in patients with FCPD than in those patients with Type 2 diabetes. PEE correlated poorly with IC. They concluded that EE in patients with diabetes varies according to the composition and distribution of body fat and is lower in patients with FCPD. Standard predictive equations were not accurate for the assessment of EE in patients with FCPD, and further research is required to recommend specific nutritional therapy for this group of patients.

Another interesting study utilizing IC was performed by Joseph *et al*.[52] which looked at thirty elite male weightlifters, aged 17–28 years, competing at the national and international levels. Anthropometric measurements and body composition were assessed. REE was measured using IC and compared with the REE predicted by eight formulas HB, Mifflin-St. Jeor, FAO/WHO/UNU, ICMR, Cunninghams, Owen, Katch-McArdle, and Nelson. The Pearson correlation coefficients between mREE and the anthropometric variables showed positive significance. All eight predictive equations underestimated the REE of the weightlifters when compared with the mREE. The highest mean difference was 636 kcal/day (Owen, 1986) and lowest difference was 375 kcal/day (Cunninghams, 1980). Multiple linear regressions done stepwise showed that lean body mass (LBM) was the only significant determinant of REE in this group of sportspersons. A new equation using LBM as the independent variable for calculating REE was computed. REE for weightlifters = −164.065 + 0.039 (LBM) confidence interval − 1122.984, 794.854. This new equation reduced the mean difference with mREE by 2.36 + 369.15 kcal/day (standard error = 67.40).

However, despite the integral role that IC has played in a number of metabolic studies, its use and full potential are yet to be realized, especially in the Indian context.

Conclusion

With continued changes in patient demographics, concurrent disease states being managed, and clinical interventions that affect metabolism, the accuracy and reliability of traditional predictive equations for determining EE are questionable. The benefits of providing optimal nutrition for recovery from illness and chronic health management have been documented. In addition, the complications associated with under- or over-feeding are often detrimental. To achieve the highest quality of patient care, we should strive for patient-specific nutrition support regimens. IC offers a scientifically based approach for customizing a patient's energy needs and nutrient delivery to maximize the benefits of nutrition therapy. Conventionally, IC has been underused, mostly due to costs, shortage of personnel, and lack of education or training. With recent advances in technology, indirect calorimeters are easier to operate, more portable, and affordable. Increased use of indirect calorimetry would facilitate individualized patient care and should lead to improved treatment outcomes. In addition, it facilitates the generation of EE data specific to different disease states, medical conditions, or patient subpopulations. Knowledge gained from these data will further refine clinical practice and also provide newer insights into the complex pathogenesis of diseases such as obesity and diabetes. This might have a far-reaching impact on the management of these diseases.

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Conflicts of interest

There are no conflicts of interest.

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