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Nutrition and Indirect Calorimetry

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Abstract

Nutrition support is important in the care of patients with both acute and chronic illness. Optimizing nutritional support for the critically ill and patients with acute and chronic respiratory disorders has been shown to shorten length of stay, shorten duration of mechanical ventilation, lower health-care costs and reduce morbidity and mortality while improving functional quality of life. Nutritional requirements are difficult to predict in patients diagnosed with cancer due to their disease processes, altered inflammatory responses and metabolic rates among many other variables. Often predictive equations are used to estimate energy requirements and the average dietary energy intake needed to maintain energy balance. Energy requirements can be estimated through the use of over 200 predictive equations. Utilization of indirect calorimetry as the 'gold standard' for measuring resting metabolic rate (RMR) and resting energy expenditure (REE) can provide support in all states of health and disease. This chapter will identify and discuss the role of indirect calorimetry, examine the reasons why indirect calorimetry is more reliable than predictive equations in determining a patient's calorie requirement, and when it is most applicable to incorporate indirect calorimetry measurements in the care of cancer patients.

Keywords: indirect calorimetry, nutrition, resting energy expenditure, predictive equations, critical illness

1. Introduction

Nutritional support is important in the care of patients with acute and chronic illness. Up to 50% of hospitalized patients are clinically malnourished, which is associated with increased infectious morbidity, increased hospital length of stay and mortality [1]. Optimizing nutri-

tional support of the critically ill and patients with acute and chronic respiratory disorders reduces morbidity and mortality, shortens hospital length of stay, shortens duration of mechanical ventilation, and lowers health-care costs while improving functional quality of life. Energy needs vary according to activity level and state of health and can vary greatly particularly in the critically ill, malnourished, postoperative and infected population. Nutritional requirements are difficult to predict in cancer patients in particular because of altered inflammatory responses and metabolic rates caused by the disease process itself. Siobal and Baltz describe a functional nutrition support system to include an interdisciplinary team approach for assessment and treatment, which incorporates an evaluation of nutritional risk, standards for nutritional support, an appropriate assessment and reassessment process, proper implementation, route of support based on patient condition, and a means of measuring nutrient requirements to determine whether target goals are being met [2].

Inflammation associated with disease/injury can cause anorexia and alterations in body composition and stress metabolism. Predominantly cytokine mediated; persists as long as the inflammatory stimulus is present. These metabolic alterations include elevated energy expenditure, lean tissue catabolism (proteolysis), fluid shift to the extracellular compartment, acute phase protein changes, and decreased synthesis of serum albumin, transferrin and prealbumin. This leads to clinical deterioration of lean body mass, poor wound healing, increased risk of nosocomial infection, weakened respiratory muscles, impaired immunity, organ dysfunction, and increased morbidity and mortality. Several studies have shown that metabolically stressed and malnourished patients have more negative outcomes and higher health-care costs. Patients with continuous energy deficits have a higher ventilator-dependence rate, longer intensive care unit (ICU) stay, and higher mortality [3–6].

2. Calorimetry

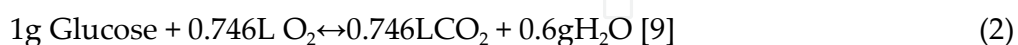
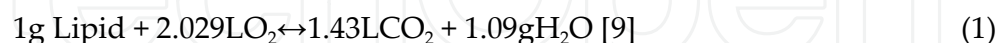
Calorimetry is a process that quantifies the heat release from metabolism of cellular fuels. It provides assessment of caloric energy present in foods and allows for measurement of energy expenditure to determine adequate calorie requirement. This information can be used for a myriad of clinical applications. Evaluating appropriate caloric intake, avoidance of overfeeding and underfeeding, and measuring caloric requirements in different disease states can be achieved through calorimetry.

It can be measured in a direct as well as an indirect manner. Direct calorimetry measures actual heat release from the metabolism of foods. This was carried out *ex vivo*. Indirect calorimetry measures metabolism of foods *in vivo*. Direct calorimetry is a challenging process that requires technical proficiency. Turell and Alexander [7] demonstrated that indirect calorimetry measurements of energy expenditure are accurate within 0.6–0.7% to direct calorimetry. In this section, the advent, mechanisms, technicalities, and limitations of indirect calorimetry are discussed.

Indirect calorimetry is able to provide information regarding metabolic rate, energy expenditure, and anaerobic thresholds. This technique has been around since late nineteenth century

[8]. Since then various advancements have been made in this field. With these advancements, it is becoming a staple of clinical medicine, particularly in the assessment of adequate caloric intake.

Indirect calorimetry measures respiratory gas exchange and estimates energy production [9]. Initially, mathematical equations modeled the metabolism of carbohydrates and lipids. These stoichiometric equations include oxygen as a reactant in conjunction with carbohydrates, or lipids. The products of this reaction are carbon dioxide and water, with heat as a byproduct.



The heat produced from these reactions can be written as

$$\text{Heat output} = 3.9(\text{VO}_2) + 1.1(\text{VCO}_2) \times 1.44 \quad [10] \quad (3)$$

VO_2 = oxygen consumption in ml/min

VCO_2 = carbon dioxide production in ml/min

1440 min/day, 1000 cal/kcal

Extracting chemical energy from cellular fuels is accomplished by completely oxidizing the substrate to carbon dioxide and water [9]. The ratio of CO_2 production to oxygen consumption is referred to as the respiratory quotient (RQ) [9]. RQ is VCO_2/VO_2 at the cellular level which is difficult to measure. Respiratory exchange ratio (RER) is VCO_2/VO_2 measured from expired air. Under steady-state conditions, the blood and gas transport systems are keeping pace with tissue metabolism, thus RER can be used as index of metabolic events and assumed to be equivalent to RQ. The test was carried out when subjects are resting. During rest, the system is noted to be under steady state. Assumptions believed to be true during indirect calorimetry measurement, aside from $\text{RER} = \text{RQ}$, are that growth is not occurring, interconversion of fuels are not occurring, and anaerobic metabolism is not occurring as it is only accurate for steady-state oxidative metabolism.

3. Protein metabolism

Measurement of protein metabolism was thought to be to clinically challenging through indirect calorimetry. In early 1900s, assumptions were made that a fixed percentage of total calories arise from the metabolism of protein, and the contribution could be ignored without effecting the estimations of energy expenditure [10]. This assumption was based on analysis of various regional diets worldwide and that on average humans consume 10–15% of their total calories as proteins [10, 11].

However, ignoring the contribution of protein metabolism does add a degree of error to the calculations. Per Turell and Alexander, a systemic error of 1.0% is introduced for each 12.3% increment in protein contribution to the total oxidative state. Varying the degree of protein intake does change the basal metabolic rate [12].

In 1948, Weir demonstrated calculations that allowed for protein metabolism to be included.

The nitrogen backbone present in all proteins is metabolized through various pathways in the human body. About 80% of nitrogen is eliminated through the kidneys as urea [13]. Hence, measuring urea excretion allows for calculation of dietary protein intake. Weir demonstrated that quantifying urinary nitrogen over a 24-hour period could then be modeled in an equation to measure contribution of protein metabolism. Hence, the equation can be written as below:

$$1\text{g Protein} + 0.966\text{L O}_2 \leftrightarrow 0.782\text{L CO}_2 + 0.45\text{gH}_2\text{O} \quad [9] \quad (4)$$

As nitrogen is noted to be 16% of protein by weight, the subsequent equation can be written:

$$1\text{g Protein} = 6.25\text{Urine Nitrogen} \quad (5)$$

The heat produced from combination of these fuel substrates can be written as:

$$\text{Heat output} = 3.9(\text{VO}_2) + 1.1(\text{VCO}_2) - 2.17(\text{Urine Nitrogen}) \times 1.44 \quad [10] \quad (6)$$

With these comprehensive changes, the RQ for various metabolic fuels can be provided.

RQ	Carbohydrate	Protein	Fat
1		0.802 [14]	0.718 [15]

Normal RQ values range between 0.67 and 1.2 while results outside of this range are suggestive of technical errors.

4. Calorimeters

Specific device and corresponding instruments are used for indirect calorimetry. The several technologies that are available require precise calibration and measurements of volume and gas analysis. The traditional device used for decades was the Deltatrac and subsequently the Deltatrac II [16]. It is the set gold standard for indirect calorimetry. Since then, other products have become available. The Quark resting metabolic rate (RMR) and CCMexpress are two such devices.

The Quark RMR metabolic meter is developed by COSMED. It is a European company based out of Italy. Quark RMR measures VO_2 , VCO_2 , and resting energy expenditure (REE). It is also

able to distinguish the different substrates being utilized. It can measure these values on spontaneously and mechanically ventilated patients.

The CCM express metabolic meter is developed by MGC diagnostics, an American company. This device also measures REE in the usual manner. It is able to perform these measurements even when inspired oxygen concentrations are above 60%, as well as with fluctuating oxygen concentrations.

These new products have been compared to the Deltatrac II, as the acknowledged gold standard. Validation trials have been performed to certify the reproducibility of these calorimeters [17–19]. Other trials have not shown similar results. The variance between the Deltatrac II and these other calorimeters has been higher than clinically acceptable [16]. The disagreement between these new calorimeters requires for further refinements for them to be used in clinical practice. These machines need to demonstrate fidelity to the set gold standard in multiple clinical settings. These settings include spontaneously breathing as well as mechanically ventilated patients. The mechanically ventilated patients are the critically sick ones [16, 20].

The M-COVX is a metabolic meter that can be fully integrated into a mechanical ventilation circuit. It is manufactured by the Deltatrac parent company [21].

MedGem is a metabolic meter that measures VO_2 alone. It makes an assumption on RQ and is for use in spontaneously ventilated patients [21].

5. Methodology

These calorimeters can be used in spontaneously breathing or mechanically ventilated patients. The inspired gas can be room air or a supplemental oxygen mixture. In a spontaneously breathing patient, an overlying canopy, face tent, or facemask can be used for gas collection. A mouthpiece with a nose clip can also be used. In mechanically ventilated patients, the calorimeter can be attached to the ventilator system. The total expired gas volume is recorded for calculations [21–25].

The several technologies that are available require precise calibration and measurements of volume and gas analysis. Although indirect calorimeters are easy to operate and understand, there are several variables that can impact accuracy in measurements. All of the devices contain gas analyzers and a flow/volume measuring device. Gas analyzers must be responsive and capable of measuring minimal changes in oxygen enriched and room air environments. The ability to measure minute changes in gas concentrations as small as 0.001% while the flow/volume measurements must be accurate across the expected clinical range is a requirement of these devices.

The principle of Haldane transformation assumes that nitrogen (N_2) is an insoluble gas and does not participate gas exchange. As a consequence, it is constant in both inspired and expired volumes. Assuming that oxygen (O_2) and carbon dioxide (CO_2) are the only gases exchanged in the lungs the inspired volume can be calculated from the expired volume [21].

Calorimeters measure inspired O₂ and CO₂ concentration, expired O₂ and CO₂ concentration, and expired gas volume. With the use of Haldane transformation, REE can be provided through indirect calorimetry. As previously stated, measuring at steady-state approximates REE to RQ.

Steady state is described as a patient under resting conditions. Many factors can effect achievement of these conditions (**Table 1**). They include but are not limited to patients undergoing physical stress such as fever and pain. Patients should be resting in a quiet room without excess environmental stimuli. Changes in the environment around the patient also affect these results [26].

30-min rest period prior (III)	Measure while room temp b/t 72–77°F (II)
Not engage in any activity during said period (V)	Measure in a quiet room (V)
For the duration of RER measurement, disregard first 5 min and then continue for at least 4 min with <10% coefficient of variation in VO ₂ and VCO ₂ and <5% for RQ (III)	At least 4 h without stimulants and 140 min without smoking (III)
Measure while supine (II)	Measure after a 7-h fast (III)
Any device ok for gas collection (III)	At least 12–48 h after light-to-vigorous exercise (V)
Measure any time of day (III)	At least 30 min rest after light activity (III)
	If RQ < 0.67 or >1.3, assume error and repeat (II)

The Academy of Nutrition and Dietetics utilizes a grading system for determining strength of evidence of studies and reports based on five factors. These factors are quality, consistency, quantity, clinical impact, and generalizability. The grading system is as follows: (I) Good, (II) Fair, (III) Limited, (IV) Expert Opinion only, and (V) Grade not assigned [27].

Table 1. Best practices for performing indirect calorimetry in healthy and non critically ill patients.

There are three areas that can pose challenges during the technical performance of indirect calorimetry. These are patient interface, elevated oxygen concentrations, and variability of mechanical ventilators. One interface for spontaneously breathing at rest subjects is a large canopy that encompasses the patients head and shoulders (**Figure 1**). This must be adapted to the subject and be free of potential leaks to prevent the loss of exhaled air. The canopy is designed to ensure collection of exhaled air close to the subjects mouth yet spacious enough for comfort and visibility. There is also an interface of a large form fitting mask that has open slots for adequate flow circulation. Another type of mask fitting is shown here (**Figure 2**). Each manufacturer identifies the ideal interface that will work well with their systems.

Many authors have described in detail about the effects of elevated oxygen on the VO₂ measurement. Branson describes an 1% error in FiO₂ measurement at 0.40 results in a 15% error in VO₂ measurement. An error effect comes into play when the FiO₂ is close to 1, and the

denominator of the Haldane equation ($1 - FiO_2$) approaches zero [28]. The impact of these variables on data results is noted in **Table 2** [28].



Figure 1. Carefusion canopy.



Figure 2. MedGraphics interface.

	VO ₂	VCO ₂	REE	RQ
Leaks	Low	Low	Low	Unchanged
Unstable FiO ₂	Low or high	Unchanged	Low or high	Low or high
FiO ₂ > 80%*	Low or high	Unchanged	Low or high	Low or high
Mixing of inspired and expired gas (active exhalation valve)	Normal or high	Low	Normal or low	Low

*VO₂ measurements are highly suspected.

Table 2. Effect of ventilator operation and ventilation issues on REE and RQ.

Performances of indirect calorimetry on subjects who are mechanically ventilated have less potential for system leaks. This closed system provides a simplified way to collect exhaled gas, and the measurement of inspired gas can be determined easily at the inspiratory limb of a ventilator circuit. The problems that arise in indirect calorimetry during mechanical ventilation are fluctuations in FiO_2 , ventilator mode, and flow requirements. The variability in FiO_2 occurs due to increased flow demands, bias flow to provide better patient interface, and high minute ventilation. Leaks can occur during mechanical ventilation due to unsealed airways or incompetent tracheal cuffs, through chest tubes or bronchopleural fistulas. Other technical aspects to consider during mechanical ventilation also include: calibration errors, recent changes in ventilator settings that may not reflect steady state, moisture in the system, patient-ventilator dyssynchrony, and acute hyperventilation or hypoventilation (impact physiologic CO_2).

Equipment variables and methodology of measuring gas concentrations can lead to inaccurate results as well. At the point of data accumulation, the issue becomes how to decrease the variance in collected data points. The variance can be due to differences in tidal volume, respiratory rate, and other patient factors [8]. These variations can lead to changes in VO_2 and VCO_2 measurements.

In order to eliminate these data variations, several techniques have been developed. They include breath averaging, time averaging, and digital filtering [8].

Breath averages collect data points over a predefined number of breaths. The average of these data points is used as the final result. Similarly, time averaging is the collection of data points over pre-designated period of time. The data accrued from all of the breaths during the pre-designated period are averaged to give one value [8].

Digital filtering removes data points that are not within a range of the median data points. In this instance, setting the range in any one direction can drastically alter the results. If the range is too high, then data points that are not necessarily precise can be included in the calculations and yield a higher/lower value than accepted. If the range is noted to be too low then many data points that are valid can be excluded from the analysis and thus providing distorted data values [8].

Recommendations exist to add correction factor estimates to decrease the error in indirect calorimetry as well. Patients can be defined as hypometabolic, hypermetabolic, and normal. Correction factors can be added for dietary thermogenesis. This is the energy required for metabolism of food. Other common correction factors are activity factors and spontaneous ventilation [29]. Recent trials are not in complete agreement with this practice. Some clinicians advocate for the removal of correction factors. They contend that correction factors lead to overfeeding. Over feeding has known deleterious outcomes in patients and this should be avoided [29]. This issue is important when dealing with patient in respiratory distress. Over feeding will lead to an increase in RQ and subsequently an increase in minute ventilation. Patients in respiratory distress will need to increase their minute ventilation at a time of respiratory compromise. This scenario is often seen in patients on mechanical ventilation. These patients will be excess nutrition that leads to them having an increase in their baseline

minute ventilation. When the time comes for spontaneous breathing trials to assess their readiness for spontaneous ventilation, they fail these trials as a consequence of overfeeding.

6. Interpretation

Measurement of indirect calorimetry is best performed with the patient at rest with a goal of achieving steady state. Steady state is characterized by <5% change from baseline measurements of the respiratory quotient (RQ), and 10%, respectively, for the VO_2 (oxygen uptake) and Ve (minute ventilation) during data collection. Nutrition, whether parental or enteral feeding, need not be held. It is recommended that the subject be at rest with minimal distractions or disturbances. Most studies consider 20–30 min of data collection an accurate reflection of 24-hour energy expenditure. Some literature also supports an abbreviated time of 5 min of steady-state data.

7. Predictive equations

While indirect calorimetry remains the gold standard for caloric assessment, predictive equations provide an alternate method of determining nutritional requirements. Given the expense associated with indirect calorimetry and advanced training required to perform accurate metabolic studies, as well as limited availability of equipment, predictive equations are a cost-effective strategy for broadly assessing metabolic requirements.

The Harrison-Benedict equation (HBE) is the most established method dating back to 1919, from studies conducted in healthy, young volunteers to assess resting energy expenditure (REE). Thus, application of these formulas in the critical care setting, particularly in the elderly, should be with caution. While utilization of these equations remains widespread, it has been noted that they may a results in a significant error in estimating REE. There have been subsequent studies attempting to refine the degree of error since the development of these equations [30, 31].

The Mifflin-St. Jeor (MSJ) equation was developed through multiple regression analyses utilizing indirect calorimetry data in a cohort of healthy men and women, encompassing a wider array of age and weights not taken into consideration in the original HBE [30, 31]. The Ireton-Jones is another equation that has been validated in trials. It has been more recently developed. It included mechanical ventilation, trauma, burns, and obesity as factors during its development and hence is more likely to be valid in these specific clinical settings [32].

Tatucu-Babet *et al.* looked at 2349 publications with 18 studies included. One hundred and sixty variations of 13 predictive equations were reviewed. Thirty-eight percent underestimated and 12% overestimated energy expenditure by more than 10% at the group level. On an individual level, the equations underestimated and overestimated energy expenditure in 13–90% and 0–88% of patients, respectively. Differences of up to 43% below and 66% above indirect calorimetry values were observed at the patient level [33].

A criticism of predictive equations is the accuracy of application to the heterogeneous critically ill patient population. These patients have continual metabolic change, which increases the difficulty of finding one prediction equation that will be accurate across the spectrum. Accuracy of these equations varies significantly, ranging from approximately 40 to 70%, where accuracy is defined as within 10% of the measured resting energy expenditure [34]. However, without the common availability of indirect calorimetry, they remain a valuable tool for widespread baseline understanding of nutritional requirement. The equation selected should be used with patients similar to the reference population from which the equation was derived.

8. Indirect calorimetry and respiratory failure

In critically ill patients, in particular those with respiratory failure, the assessment of adequate nutrition is paramount. Respiratory muscle strength begins to decline after a few days of suboptimal nutrition [35]. Supplemental nutrition and overfeeding can increase oxygen consumption and carbon dioxide production, which can have deleterious consequences in patients with a limited ability to augment their ventilation. This can result in the need for mechanical ventilation and may make ventilatory management and weaning difficult. In a study of 213 ventilator-dependent patients, approximately 25% received calories within 10% of measured energy expenditure; 32–93% were overfed, and 12–36% were underfed [36]. Patients' energy needs predicted from equations compared to those measured via IC were 2× as likely to develop a negative energy balance associated with longer ventilator dependence [37]. An increasing RQ significantly correlated with increased respiratory rate and decreasing tidal volume, indicating rapid-shallow breathing and ventilatory compromise [38]. Adequate feeding significantly correlates with duration of ventilator dependence ($r = 0.494$, $p = 0.03$) and ICU stay ($r = 0.525$, $p = 0.02$) [39].

9. Indirect calorimetry and malignancy

There are limited studies of indirect calorimetry in the cancer population, especially with respects to the critically ill patient population. Garcia-Peris *et al.* looked prospectively at changes in resting energy expenditures measured by indirect calorimetry in patients with head and neck cancers treated with chemoradiation. They found the REE changed significantly. Compared to the Harris-Benedict equation, REE was represented by a U-shaped curve over time, as compared to a decreasing line by Harris-Benedict. Further, Harris-Benedict significantly underestimated REE before and at the end of treatment [40]. Reeves *et al.* looked at resting energy expenditures in solid tumor patients undergoing therapy. They found the fat-free, mass-adjusted REE was not significantly different between cancer patients and healthy patients, and the limits of agreement were wide for all prediction methods, up to 40% below and 30% above measured REE [41]. Johnson *et al.* compared measured and predicted resting energy expenditures in 33 cancer patients divided in weight-stable and weight-losing group-

ings. They found no difference in measured REE between the groups. However, the Harris-Benedict equation predicted REE was within clinical acceptable limits for only 61% of weight-losing and 56% of weight-stable patients, respectively [42].

In those patients with malignancy and critical illness, the accuracy of the predictive equations may be even more skewed, as this specific patient population has not been well studied. Further, the metabolic demands of a patient may be affected by cancers of different sites-of-origin, different cancer cell subtypes, different stages of disease, as well as a history of prior/ongoing chemotherapy and radiotherapy. As such, indirect calorimetry at an individual point and trended over time may be a more accurate reflection of one's nutritional needs.

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