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Indirect Calorimetry in Mechanically Ventilated Patients to Assess Nutritional Targets

An overview of the physiological aspects of indirect calorimetry, its limitations in use, the available literature and future prospects for tailored nutrition.

Introduction

Medical nutrition therapy (MNT) is an essential part of patient care in the intensive care unit (ICU) setting. Similar to mechanical ventilation and haemodynamic management, nutritional intake should be individualised for each patient. Achieving energy and protein targets should be a daily concern for the ICU physician. Indeed, it is currently established that the accumulation of an energy debt is associated with an increase in morbidity and mortality in the ICU (Villet et al. 2005). In addition, insufficient protein intake may contribute to the development of ICU-acquired muscle weakness (De Janghe et al. 2009). These disabling functional sequelae may persist over the long term (Herridge et al. 2011). On the other hand, the provision of excessive artificial nutrition or 'overfeeding' may lead to infectious or metabolic complications (Elke et al. 2014; Weinsier et al. 1981).

It therefore seems pragmatic to tailor the daily intake of patients to their precise nutritional needs. These can vary significantly over the course of a stay, according to the patient's age, pre-existing comorbidities and the severity of their condition. Historically, the assessment of the energy expenditure in the ICU was based on equations that included clinical and anthropometric data. Most of these were developed for healthy subjects to which a stress factor was applied. These assessments turned out to be highly inaccurate when compared to actual measurements in a study published in 2003. In this work, Harris and Benedict equation developed in 1918 was providing only 60% of actual energy requirements in critically ill patients (MacDonald and Hildebrandt 2003; Harris and Benedict 1918). Another strategy recommended by international guidelines was the use of fixed energy targets around 25 kcal/kg/day for ICU patients (Lefrant et al. 2014; McClave et al. 2015). However, this simplistic solution, which is supposed to suit everyone, does not take into account the individuality of patients and their specific characteristics. Given these inaccuracies, the ESPEN recommendations, published in 2018, have reshuffled the deck (Singer et al. 2019). The recommended technique for assessing nutritional requirements has evolved into the measurement of energy expenditure based on indirect calorimetry. This recommendation was made possible by technological advances allowing the development of more reliable and ergonomic tools available to the ICU physician (Oshima et al. 2020; Rehal et al. 2016). In this review we will discuss the physiological aspects of the technique, its limitations in use, the available literature and the future prospects for tailored nutrition.

Physiological Principles

The energy target is determined by the energy expenditure which can be assessed in several ways. Direct calorimetry measures heat production but require an insulated chamber which makes it unsuitable for daily patient care. Indirect calorimetry is the gold standard method for estimating energy metabolism based on gas exchange analysis. Indeed, the oxidation of substrates results in the production of energy, in the form of adenosine triphosphate, nitrogen and water. Estimating resting energy expenditure (REE) through indirect calorimetry relies on the measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2). The use of the Weir formula can therefore be applied with the help of urinary nitrogen that reflects protein oxidation.

$$\textbf{EE (kcal/day)} = 1.44 \times [3.94 \times VO_2\text{(ml/min)} + 1.11 \times VCO_2\text{(ml/min)}] - \text{urinary nitrogen (g/day)} \times 2{,}17$$

According to the Haldane transformation principle, nitrogen is inert and its concentration is the same in the gas inspired and exhaled by the patient. This observation eliminates the need for urine sampling which can be unreliable in ICU patients. This customisation raises the error level to less than one percent (Wilmore and Costill 1973; Weir 1949).

$$\textbf{EE (kcal/day)} = 1.44 \times [3.94 \times VO_2\text{(ml/min)} + 1.11 \times VCO_2\text{(ml/min)}]$$

Indirect calorimetry also allows the measurement of the respiratory quotient (RQ) which estimates the type of substrate consumed such as carbohydrates, proteins and lipids. This ratio is measured between 0.67 and 1.3 in humans. The ratio is close to 1 for carbohydrate metabolisation, 0.8 for protein and 0.7 for lipids.

$$\mathbf{RQ = VCO_2/VO_2}$$

By assigning the respiratory quotient to an average of 0.86 or estimating it from the nutritional intake (food quotient or nutritional quotient), energy expenditure can be estimated based on the production of carbon dioxide alone. This method, derived from indirect calorimetry, is a fair compromise that is more accurate than predictive equations but less than exhaustive indirect calorimetry (Stapel et al. 2015; Oshima et al. 2017; Kagan et al. 2018).

$$\mathbf{FQ = \%_{protein} \times 0.8 + \%_{carbohydrates} \times 1 + \%_{lipids} \times 0.7}$$

$$\mathbf{EE\ (FQ)\ (kcal/day) = 1.44 \times [3.94 \times VCO_2(ml/min)/FQ + 1.11 \times VCO_2(ml/min)]}$$

$$\mathbf{EE_{(RQ = 0.86)}\ (kcal/day) = VCO_2(ml/min) \times 8.19}$$

Even if the process is fully automated, the knowledge of these formulas allows a better understanding of the functioning of the indirect calorimetry machines but also of their limitations.

Indication, Repetition and Limitation

The 15th recommendation of 2019 ESPEN guidelines, which was accepted with strong consensus, states that in critically ill mechanically ventilated patients, energy expenditure should be determined by using indirect calorimetry. This decision has greatly expanded the scope of calorimeters in the ICU and has led to an evolution in our nutritional practices towards tailored prescriptions and goal-oriented therapy (Singer et al. 2019).

Nevertheless, this technique has several limitations linked with all situations that can disturb the measurement of gas exchange. The first prerequisite for reliable measurements is the stability of the patient's clinical condition. This implies the absence of sudden haemodynamic or respiratory parameters variations. The second limit relies on respiratory parameters that may interfere with the gas analyser including an inspired oxygen fraction (FiO_2) higher than 70%, a respiratory rate higher than 35/min or a positive end expiratory pressure higher than 10 cmH_2O. Furthermore, the presence of any type of air leaks in the ventilator circuit or within the patient respiratory tree (bronchopleural fistula or chest drainage) may result in an underestimation of the energy expenditure.

> **ESPEN guidelines state that in critically ill mechanically ventilated patients, energy expenditure should be determined by using indirect calorimetry**

Finally, any variation of CO_2 stock may impair IC functioning. Continuous renal replacement therapy (CRRT) is a known factor that may cause CO_2 extraction or metabolic shift via fluid dynamics or citrate use. A recent clinical trial published by Jonckheer et al. (2020) have questioned this relative contraindication. They measured CO_2 content in the CRRT effluent liquid to estimate and correct the 'true VCO_2' used in the Weir equation. Surprisingly, the use of CCRT accounted for less than 2-3% of REE measurement error. The use of a correcting factor was then considered irrelevant (Jonckheer et al. 2020). In the same field, in critically ill patient benefitting from an extracorporeal membrane oxygenation (ECMO) therapy, Wollersheim's team suggested in a recent paper the use of the MEEP protocol to correct energy expenditure measurements based on pre- and post-membrane blood gas (Wollersheim et al. 2018).

Despite these few precautions and adjustments, use of IC remains possible in the majority of ICU patients. However, it is important to note that the measurement of energy expenditure is a reflection of energy metabolism at a given time. This value can vary significantly from one hour or one day to the next. Therefore, longitudinal assessment is advised during the ICU stay and when significant changes in clinical status occurs (Vermeij et al. 1989). For example, the incidence of sepsis was associated with a 30% increase in metabolic rate in a landmark study published in 1993 (Kreymann et al. 1993). The degree of hypermetabolism in the acute phase of severe sepsis was even associated with 28-day mortality in the ICU setting (Wu et al. 2015). This observation seems plausible given that energy expenditure is a direct reflection of the systemic inflammatory exacerbation associated with the secretion of proinflammatory cytokines and neurohormonal response. Moreover, in a study published in 2020, Li et al. demonstrated the feasibility of using indirect calorimetry to assess the metabolic capacity of nutrient assimilation in septic critically ill patients. The ability of the organism to metabolise carbohydrates after the introduction of enteral nutrition was associated with better survival in the ICU (Li and Mukhopadhyay 2020).

In addition to sepsis, other known factors have been identified for their impact on the measures (Mtaweh et al. 2019). Apart from clinical constants such as temperature, minute ventilation and heart rate, therapies inherent to organ failure management may affect calorimetric measurements. The administration of neuromuscular blocking agents is a known influencing factor. A recent cohort study observed a significant decrease in energy expenditure in mechanically ventilated patients treated with continuous infusion of cisatracurium (Koekkoek et al. 2020). The same findings were observed with the use of deep sedation such as midazolam or analgesia with opiates in ICU patients (Swinamer et al. 1988; Terao et al. 2003). Furthermore, obese patients have very heterogeneous energy requirements, even with identical body mass index. The use of adjusted body weight, recommended by various experts groups, can regularly be associated with an overestimation of actual needs (Ridley et al. 2020). This justifies conducting repeated measurements of energy expenditure and paying particular attention to the prevention of skeletal muscle loss.

The value of longitudinal measurement has been highlighted recently by the LEEP-COVID project coordinated by Paul Wischmeyer's team, whose preliminary results have been published. In 22 patients with severe COVID, repeated measurements of energy expenditure showed high, rising and persistent hypermetabolism for up to three weeks after intubation (Whittle et al. 2020). This prolonged metabolic exacerbation could explain the muscle damage and the severity of functional sequelae in COVID survivors (Van Aerde et al. 2020). The underestimation of actual energy expenditure was already known in other pathologies associated with marked systemic inflammation such as acute pancreatitis or peritonitis (Valainathan et al. 2019; Plank et al. 1998). These measured values, sometimes far above the expert recommendations for caloric provision, raise concerns and may justify broader use of indirect calorimetry. Furthermore, this great variability in daily values goes against the pattern historically described by Cuthbertson in 1942 of an initial 'ebb phase' followed by a 'flow phase' supposed to describe the majority of intensive care stays (Cuthbertson et al. 1942). The day-to-day use of calorimetry not only allows us to adapt nutritional intake to the real needs of critically ill patients, but also to understand more accurately their metabolic patterns resulting from the progression of their condition.

From Energy Expenditure to Caloric Target

ESPEN guidelines state that if indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness. During the early phase, it is suggested to administer hypocaloric nutrition not exceeding 70% of EE and slowly increase up to 80-100% after day 3 (Singer et al. 2019).

This recommendation is based on a recent study by Zusman et al. (2016) analysing data from 1171 patients who benefitted from energy expenditure measurements by indirect calorimetry. A ratio of administered calories to energy expenditure between 60% and 80% was associated with the lowest mortality, length of stay and duration of mechanical ventilation. This result is consistent with the findings of Arabi et al. (2015) who demonstrated the non-inferiority of a permissive, normo-protein hypocaloric strategy in the first week of the ICU stay.

> **the measurement of energy expenditure via indirect calorimetry constitutes a major advance in the era of individualised evidence-based medicine**

The gradual increase in energy target during the acute phase makes sense since the initial caloric intake adds to the endogenous production of energy from proteolysis, lipogenesis and gluconeogenesis. Excessive initial intake would be considered as overfeeding, which is known to be associated with metabolic and infectious complications.

Benefit on ICU Outcomes

The main focus in the last few years has been to determine whether monitoring energy expenditure and providing individualised nutritional prescriptions can improve the outcome of intensive care patients.

In 2011, Singer et al. published one of the landmark studies investing indirect calorimetry. This randomised controlled trial included 130 mechanically ventilated patients with a length of stay greater than 3 days. Daily caloric intake was prescribed according to energy expenditure assessed by indirect calorimetry or based on a fixed dose of 25 kcal/kg/day. Regarding in-hospital mortality, the primary endpoint, a trend in favour of indirect calorimetry guided strategy was observed ($p=0.058$). Nevertheless, there was a significant reduction of the length of stay and duration of mechanical ventilation (Singer et al. 2011). The TICACOS international follow-up study was published in 2021 and included 7 sites and 417 patients. The use of energy expenditure measurement compared to a fixed target significantly increased caloric and protein intakes without significantly influencing morbidity and mortality in participants (Singer et al. 2021).

The EAT-ICU study published in 2017 aimed to demonstrate the superiority of 'early goal' approach management with an early achievement of caloric targets estimated by indirect calorimetry. Unfortunately, this strategy was not associated with any benefit on the mental or physical outcome of the participants (Allingstrup et al. 2017).

A recent meta-analysis published in 2021 by Duan et al. included eight randomised controlled trials evaluating the clinical impact of energy prescription based on expenditure measurement by indirect calorimetry. A significant beneficial effect on short-term mortality was found in the 991 critically ill patients included. However, no significant effect was observed regarding duration of mechanical ventilation and length of stay (Duan et al. 2021).

Several reasons may be suggested to explain the lack of clear evidence of the benefit of indirect calorimetry guided nutrition in the literature. On one hand, an individualised assessment of nutritional needs is maybe not necessary for all critically ill patients including short stays and illnesses associated with low nutritional risk. Heyland et al. (2011) developed the NUTRIC score in order to distinguish the patients who would benefit most from optimising their nutritional intake. One line of research could be to assess the impact of individualised nutrition based on indirect calorimetry in at-risk patients with a NUTRIC score strictly higher than 4.

On the other hand, individualised energy target alone may not be sufficient to influence patient outcome. The answer may lie in the importance of the proportion of calories related to protein intake. Several methods are available to the ICU physician for estimating anabolic/catabolic balance and skeletal muscle loss. The most frequently cited technique in the literature is the measurement of the nitrogen balance calculated from the difference between excreted (urinary and non-measurable) and ingested nitrogen; the result is obtained from the analysis of 24-hour urine (Danielis et al. 2019). Nevertheless, its measurement may be affected by the occurrence of renal failure or major fluid movements. Bio-impedance and radiological measurements by ultrasound or tomography are paths of research to explore in the longitudinal follow-up of our critically ill and post-ICU patients (Thibault et al. 2016; Pardo et al. 2018; Dusseaux et al. 2019). None of these techniques have yet shown clear benefit in guiding the prescription of tailored protein intakes. Until a reliable, repeatable, non-invasive technique is available, ESPEN advises progressive prescription of protein intake with a target of 1.3 g/kg/day (Singer et al. 2019). This progressive approach seems crucial in view of a study published in 2019 which demonstrated better survival in patients receiving less than 0.8g/kg/day before D3 and more than 0.8g/kg/day after 3 days (Koekkoek et al. 2019).

Finally, the choice of endpoints considered to be sufficiently hard, such as mortality and length of stay, may not be the most appropriate for the evaluation of nutritional practices. In this field, the selection of a functional primary endpoint was very rare in a recent pragmatic study (Taverny et al. 2019). However, this observation seems to be challenged in recent studies such as EAT-ICU where the primary endpoint was the physical component of the SF-36 quality of life score (Allingstrup et al. 2017). Similarly, in an ongoing trial evaluating the combination of physical exercise and high-protein intake, the primary endpoint is physical functioning at hospital discharge (Heyland et al. 2019).

Conclusion

The spread of the measurement of energy expenditure via indirect calorimetry constitutes a major advance in the era of individualised evidence-based medicine for each patient. The development of longitudinal monitoring of metabolic activity and the evaluation of substrate consumption via the analysis of the respiratory quotient are promising aspects that should be the subject of future clinical trials. Large-scale trials evaluating the impact of indirect calorimetry on functional endpoints would certainly contribute to the debate. Moreover, the conduct of medico-economic studies justifying the purchase of these expensive machines would constitute a strong signal for the future of critically ill patient nutrition care (Arabi et al. 2017). In the meantime, given its ease of use when available, bedside use of indirect calorimetry should be encouraged to move towards personalised medicine in the intensive care unit.

Conflict of Interest

None. ■

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