Towards optimal nutrition in the critically ill

Stapel, S.N.

2019

document version
Publisher's PDF, also known as Version of record

The principal goal of nutrition support in the critically ill is to minimize the loss of lean body mass, to maintain an adequate nutritional status, and to ultimately achieve better patient outcome. The research described in this thesis was conducted with the aim to optimize nutrition in critically ill patients.

Chapter 1, the introduction, provides an overview on important aspects of nutrition in critically ill patients. The metabolic stress response and the different phases of critical illness are described. A background is provided on the assessment of energy expenditure, the assessment of body composition, and on the role of nutritional protein in the critically ill. Finally, the aims and outline of this thesis are given.

Part I - Assessment of energy expenditure (EE) in the critically ill

Measurement of EE by indirect calorimetry is recommended to guide nutrition. However the current gold standard metabolic monitor for intensive care patients, the Deltatrac® metabolic monitor (Datex, Helsinki, Finland), is no longer in production and its use is time and resource consuming. Therefore, in clinical practice equations are used to estimate EE, which have repeatedly shown to be inaccurate. In indirect calorimetry, EE is calculated from measured oxygen consumption (VO_2) and carbon dioxide production (VCO_2) using the Weir equation. Most modern ventilators measure VCO_2 continuously, and when the respiratory quotient, the ratio of VCO_2 to VO_2 (RQ) is assumed, EE can be calculated with the rewritten Weir equation (EE-VCO_2). In **chapter 2**, we tested the accuracy of EE-VCO_2. We performed simultaneous 24-hour measurements of VCO_2 from the ventilator and of EE by indirect calorimetry (EE-IC) in 84 mechanically ventilated critically ill patients and used the RQ of the actual nutrition to calculate VO_2 and EE. We found that EE-VCO_2 was accurate, with a bias of 7.7%, and more precise than frequently used predictive equations. EE-VCO_2 appeared as the best alternative to indirect calorimetry. The most important message of the study is that EE can be estimated at the bedside as 8,19*VCO_2 (ml/min). This message is especially important for ICUs that do not have access to indirect calorimetry. Furthermore, using VCO_2-derived EE allows for continuous measurement of EE, which may be important in critically ill patients with variation of EE over time. Main limitation of the VCO_2 method is that an RQ has to be assumed in order to derive the unknown oxygen consumption needed to calculate EE according to the Weir equation. EE-VCO_2 has other limitations as well, we also found that EE-VCO_2 derived from the ventilator was systematically higher than from the Deltatrac and that the largest differences between EE-VCO_2 and EE-IC were noted in patients with extreme variations in respiratory rate and tidal volume. This is probably caused by inaccuracies in the synchronization of flow and volume for analysis. Thus, EE-VCO_2 should probably not be used in patients with irregular and rapid breathing patterns.

In **chapter 3**, we respond to a database study by Oshima et al., that evaluated whether VCO_2 based EE could be considered as an alternative to indirect calorimetry. In

their retrospective study they found a low bias of 1.1%. However, based on low 5% accuracy rates of 49% they concluded the agreement was not sufficient to consider VCO_2 based EE as an alternative to indirect calorimetry. In our letter to the editor we agreed with the authors that indirect calorimetry remains the gold standard for assessment of EE in mechanically ventilated patients. However, in spite of its known limitations, we emphasize that VCO_2 based EE appears to be the best alternative for clinicians not having access to indirect calorimetry and underscore its superiority to predictive equations. We refer to several prospective studies for evidence, including the one presented in chapter 2. We however, share the opinion of the authors that a new accurate, easy to use and affordable indirect calorimeter for the critically ill population is needed.

Chapter 4 features the results of a comparison of a new breath-by-breath indirect calorimeter, the E-sCOVX (GE Healthcare, Helsinki, Finland), to the reference method Deltatrac□. EE was measured simultaneously with the E-sCOVX and the Deltatrac□ for two hours and agreement was tested. The performance of the E-sCOVX was also compared to predictive equations. A total of 29 measurements in 16 patients were performed. The agreement between E-sCOVX and Deltatrac□ was poor, with a clinically unacceptable bias of 12.1 % and wide limits of agreement. Our findings were in accordance with other studies that have shown overestimation of EE measured by breath-by-breath metabolic monitors, such as the Quark and V-max, compared to the Deltatrac□ (1-4). In this chapter, we provide explanations for the inaccuracy of breath-by-breath methods in critically ill patients. The inaccuracy probably results from inaccuracies in the synchronization of flow and volume for analysis. Critically ill patients may exhibit rapidly changing breathing patterns, especially in assisted ventilator modes. In the presence of rapid breathing or a short breathing cycle the synchronization of flow and volume becomes less accurate. In contrast to breath-by-breath methods, the Deltatrac□ uses a mixing chamber, which may explain its superiority.

Part II - Assessment of body composition in the critically ill.

Assessment of body composition seems important for the identification of patients who are at nutritional risk and have limited physiologic reserve. Bioelectrical impedance analysis (BIA) is a simple, non-invasive, bedside technique that estimates body composition. BIA measures the opposition to an alternating current while passing through body compartments (resistance) and the delay in conduction by cell membranes (reactance). The composite marker phase angle (calculated as arc tangent (reactance/resistance) * 180°/π), reflects cellular mass and the integrity of cell membranes. Phase angle is proposed as a marker of cellular health and has appeared as a predictor of morbidity and mortality in various patient groups (5, 6). We hypothesized that a low phase angle on ICU admission is a predictor of long-term outcome and that measuring phase angle can aid in risk assessment of patients on ICU admission. In **chapter 5**, we report the results

of a prospective observational study in 196 patients in whom we tested whether phase angle as measured by BIA on ICU admission independently predicts 90-day mortality. We found that low phase angle was associated with mortality, independent of validated ICU risk scores. ICU patients with a phase angle below 4.8 had a 3.7 times higher adjusted risk of dying within 90 days. Previous studies in critically ill patients have shown the predictive value of phase angle on 28-day and hospital mortality (7-10) . Our results suggest that phase angle has even stronger discriminative power when used for prognostication beyond 28-day mortality. The survival curves in our population showed a substantial late mortality in patients with low phase angle, underscoring the potential of phase angle as a predictor of late mortality. Identification of these patients with limited physiological reserve is important to guide preventive and supportive measures. In addition, phase angle seems an interesting biomarker to monitor targeted interventions aiming to improve long-term outcome of ICU-patients.

It should be noted that the phase angle cut-off value of 4.8 was derived from the studied patients. Ideally, the cut-off value should be prospectively validated. Furthermore, phase angle is a function of resistance and reactance and changes with altering hydration status. Large fluid shifts before ICU admission or during the first hour of ICU stay could cause changes in phase angle. In that case low phase angle does not only reflect low body cell mass but also the consequences of increased hydration. Nevertheless, low phase angle on ICU admission, whether due to poor cellular health or fluid overload, seems an interesting biomarker of physical health.

In the critically ill, low muscle mass and quality on ICU admission, as assessed by muscle area and density on CT-scan at the level of the third lumbar vertebra, are associated with poor outcome (11-17). However, using CT-scan analysis for assessment of muscle mass and -quality has several limitations, including radiation exposure, costs, risks associated with patient transport, and time consumption. BIA also assesses muscle mass and is an attractive technique because of its ease of use at the bedside. However, the main limitation of both BIA and CT is that they assess muscle mass indirectly. Both rely on equations to convert the raw parameters (CT: muscle area and muscle density, and BIA: resistance, reactance, phase angle) to muscle mass. These equations are not validated in the critically ill with increased hydration and an unreliable body weight. Nonetheless, a recent study in Asian critically ill patients showed agreement and a high correlation between BIA and CT-derived muscle mass (18). Therefore, BIA may be a potential tool to assess low muscle mass in critically ill patients. However, further validation of the raw and calculated markers of muscle mass as assessed by BIA and CT in the Caucasian population is needed.

In **Chapter 6**, we report the results of a prospective observational study in 110 ICU patients in whom we compared CT-derived muscle mass and BIA-derived muscle mass and tested the ability of BIA to identify patients with low muscle mass on CT-scan.

We also determined the relation between the raw BIA markers (resistance, reactance, phase angle) and the raw CT measurements (skeletal muscle area and skeletal muscle density).

We found that all three BIA-derived muscle mass equations showed a proportional bias compared to CT-derived muscle mass with increasing disagreement at higher muscle mass. However, in the lower muscle mass range, agreement was better. Importantly, BIA had good discriminative capacity to identify patients with low muscle mass on CT-scan. Since this is the population at risk for adverse outcome, BIA might be a clinically useful tool for identification of patients at risk; not only by using phase angle (chapter 5) but also by identification of low muscle mass. Interestingly we also found that muscle density on CT-scan, proposed as a marker of muscle quality, correlated with phase angle, a proposed marker of cellular health, and that CT-derived muscle area and density were significantly lower in the patients with a phase angle lower than 4.8, the mortality-related cut-off value, as found in our previous study (chapter 5), compared to those with higher phase angle. The significant relation between the primary measured markers of BIA and CT are therefore of clinical interest.

Part III - The role of protein in critical care nutrition

Not only the amount of nutritional energy (kcals), but also the amount of nutritional protein seems important for outcome in critically ill patients. Optimal protein nutrition aims at limiting the loss of muscle and other lean body mass during the catabolic state and at restoring the protein pool during the anabolic phase. **Chapter 7** reports a prospective observational cohort study in 886 mechanically ventilated patients undergoing indirect calorimetry aimed to investigate the effect of reaching personalized energy and protein targets on clinical outcome. Targets were: the provision of energy meeting energy expenditure assessed by indirect calorimetry + 10%, as well as a protein provision of more than 1.2 grams per kg preadmission body weight. Cumulative energy and protein intakes were calculated for the entire period of mechanical ventilation and patients were categorized in four groups based on whether energy and protein targets were reached or not. We found that reaching both energy and protein target was independently associated with a decrease in 28-day mortality by 50% compared to when neither target was reached which remained after adjustment for confounders. Whereas only reaching energy targets was not associated with a reduction in mortality. The group of patients in which only the protein target was reached was too small for analysis. Main limitation of our study is the observational design; thereby a cause-effect relationship cannot be shown. These results are however hypothesis generating.

Acute kidney injury is a frequent manifestation of critical illness, and continuous venovenous hemofiltration (CVVH) is commonly used as renal replacement therapy (RRT) modality. During RRT, amino acids are lost via the filter membrane and a higher protein

intake may be warranted. Previous studies showed considerable losses of amino acids in the ultrafiltrate during CVVH. During CVVH solutes are not only removed by filtration, but also by adsorption to the filter membrane. We aimed to investigate the loss of amino acids during CVVH with a modern polysulfone filter and to differentiate between the loss by ultrafiltration and by adsorption. We hypothesized that apart from loss by UF there would also be loss by adsorption to the filter membrane. In **Chapter 8**, we report an observational study in ten patients treated by predilution CVVH and measured the loss of amino acids by adsorption to the filter membrane and by ultrafiltration. We found an estimated amino acid loss of 13.4 g/day, corresponding to a loss of about 11.2 g of protein per day. This loss corresponded to 20% of the amount of protein administered by nutrition. Adsorption did not play a major role. However, individual amino acids behaved differently, suggesting complex interactions and processes at the filter membrane or peripheral amino acid production. Limitations were the small sample size, the use of arterial samples to calculate prefilter concentrations, and the assumption of a constant blood flow and predilution flow. However, the consistency of our findings over time and the concordance with findings in other studies supports the reliability of our results. In patients treated by CVVH it seems therefore rational to increase daily protein intake by 10-15 grams to compensate for the loss of amino acids provided that liver failure or other disturbances in protein handling is not present.