Quest for the Best

Safety and Optimization of Nutrition Therapy during Critical Illness and Convalescence

Rianne Slingerland-Boot

Propositions

1. Nutritional prescriptions not based on indirect calorimetry are potentially harmful in (post-)Intensive Care Unit patients.
   (this thesis)

2. Continuing enteral feeding should become the standard of care for *all* post-Intensive Care Unit patients until they have proven to have sufficient oral nutritional intake.
   (this thesis)

3. Researchers in peripheral hospitals require academic collaboration to publish in Q1 journals.

4. Having found the right balance between application of evidence based practice and practice based evidence makes you a good doctor.

5. The branded antidiabetic drug Ozempic® (semaglutide) should not become cheaper on the Dutch market.

6. Research-generated medical information and its interpretation by experts should become as easily accessible as the medical nonsense that is omnipresent on social media platforms.

Propositions belonging to the thesis, entitled

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Quest for the Best:

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Thesis

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CHAPTER 1

1

General Introduction

1. Background

Annually over 85.000 patients are admitted to Dutch Intensive care units (ICUs), a number expected to increase with an ageing population living longer with more chronic conditions (1). Even though the number of ICU survivors has steadily increased over the past decades, little is known about their long-term health. Despite the observed reduction in ICU mortality, the long-term consequences of ICU admission are a growing concern as more patients are dismissed to rehabilitation centres. Moreover, an increase in physical and functional disabilities with a decrease in quality of life (QoL) has been reported (2-4). Many ICU survivors suffer from prolonged physical, mental and cognitive health problems, and even for ICU survivors who do not experience these issues, (complete) recovery can take an unexpectedly long time. These observations may lead to the question: *"Are we creating survivors… or victims in critical care?"* (2).

Nonetheless, there are minimal evidence-based therapies to enhance recovery and thus optimise QoL in the post-ICU convalescence (5,6). Undoubtedly, recovery after the acute phase of critical illness can only be accomplished with adequate nutrition, particularly proteins. However, the disrupted metabolism (including mitochondrial dysfunction) during critical illness has implications for nutrition therapy. Therefore, this thesis aims to increase knowledge about the nutritional journey of critically ill patients in the ICU and post-ICU period, with the ultimate goal of improving current nutritional strategies and preventing adverse effects.

In this thesis several aspects of nutritional therapy during ICU stay were investigated, including some metabolic interactions of macronutrient administration during refeeding syndrome. In addition, the evolution of mitochondrial dysfunction during sepsis was studied, as well as the impact of continuous sedation (which in vivo suppresses mitochondrial function) on clinical outcomes, as this has consequences for nutritional support. Finally, it was examined what happens to nutrition during the post-ICU hospitalization period, including possible associations with clinical outcomes.

2. (Sustained) ICU-AW and PICS

Many patients in the ICU suffer from critical illness myopathy (CIM), critical illness polyneuropathy (CIP) or a combination of CIM and CIP, known as ICU-acquired weakness (ICU-AW) (6-8). ICU-AW is clinically defined as a generalised significant muscle weakness, typically symmetrical and affecting limb and respiratory muscles, with no other plausible etiology than the underlying critical illness and its treatment (6-9). Several risk factors have been identified, including non-modifiable (such as the severity of illness and

duration of mechanical ventilation) and modifiable factors (including hyperglycemia and dose and duration of medication administered) (7,8). Once ICU-AW is suspected, it is most commonly diagnosed using clinical examination and electrophysiological assessments (6-9). The exact prevalence of ICU-AW is unknown as numbers vary widely and depend on the population studied, timing and method of assessments and pre-ICU functional status (including age-related frailty) (7,8). A systematic review by Fan *et al.*, evaluating 31 studies (including 3,905 patients), observed a median prevalence of 43%, although a broad interquartile range (25-75%) was reported (10).

ICU-AW has been associated with several short-term clinical outcomes, such as increased duration of mechanical ventilation, prolonged ICU and hospital length of stay and higher ICU and hospital mortality (7,10,11). Moreover, in the mid-to-long term, ICU-AW is related to sustained reduced physical functioning, a higher chance of being discharged to rehabilitation centres or nursing homes, and an increased risk of one-year mortality (7,11).

In the post-ICU convalescence, the experienced prolonged physical, mental and/or cognitive impairments are part of the post-Intensive Care Syndrome (PICS). Common complaints are protracted muscle weakness (also known as sustained ICU-AW), reduced exercise tolerance, dyspnoea, pain, anxiety, post-traumatic stress symptoms, depression, sleep disturbances, and loss of attention and memory (12,13). These problems are encountered frequently (current literature reports up to 80%). However, the exact prevalence of (the elements of) PICS is (are) also unknown as rates vary widely and symptoms are often un(der)recognised (1,12-14). In a study by Meyer-Frieβem *et al.*, interviewing 149 ICU survivors up to ten years post-ICU discharge, about 75% of the survivors experienced symptoms of sustained ICU-AW. However, only 11.6% had been officially diagnosed with ICU-AW (15).

The multidimensional PICS-related disabilities have an extensive impact on patients' and their families' lives, including socio-economic status and experienced QoL, and may last up to ten years (12,14-18). At one year post-ICU discharge, more than 50% of the ICU survivors experience restrictions in daily functioning, requiring any form of caregiver assistance (14,19). Moreover, only about 50% of the patients can resume employment within one year after discharge (14,19). In addition, ICU survivors have an increased risk of rehospitalisation (16.2% within 30 days and 18.9% within six months), with high rates of ICU readmission and hospital mortality (20).

The pathophysiologies of ICU-AW and PICS have not been fully unravelled yet but are multifactorial, with significant skeletal muscle loss (2.1) and muscle dysfunction (2.2) contributing to the observed physical disabilities in these patients (4,18,21-23).

In PICS, (prolonged) mitochondrial dysfunction is likely to play a pivotal role, as described in *Mitochondrial (dys)function in health and critical illness* (24).

2.1 Skeletal muscle mass loss

In the early course of critical illness, predominantly during the first week of ICU stay, patients experience rapid muscle wasting. They may even lose up to a kilogram of lean body mass daily, making them prone to ICU-AW (2,21,22,25). The pathophysiology behind this rapid muscle wasting is a change in protein homeostasis, predominantly favouring muscle proteolysis (amongst others via the ubiquitin-proteasome pathway) and a reduction in muscle protein synthesis in the early acute phase (5,22,26,27). This metabolic stress state in critically ill patients is part of an adaptive response to provide sufficient energy substrates to vital tissues to survive acute illness (25). Stress hormones and inflammatory cytokines induce hypermetabolism, resulting in endogenous energy production, such as gluconeogenesis by the liver. Additionally, alternative substrates, such as amino acids from increased muscle proteolysis, are used (3,25).

2.2 Skeletal muscle dysfunction

In addition to progressive muscle loss, multiple factors contribute to the loss of muscle function during critical illness. These include, amongst others, fatty infiltration and fibrosis of muscles, microcirculatory changes decreasing perfusion and oxygen delivery, impaired activation of autophagy, ion channel dysfunction, and muscle disuse (7,28). Furthermore, mitochondrial dysfunction (bio-energetic downregulation) may play a role in ICU-AW development (24). Mitochondrial dysfunction has been demonstrated in various cells in septic ICU patients, including muscle tissue, peripheral blood mononuclear cells and blood platelets (29-32). The earliest signs of mitochondrial dysfunction may be observed within the first 24 hours of ICU admission and may continue to be present for years after hospital discharge (29,33). Mitochondrial (dys) function in health and critical illness will be discussed in detail below.

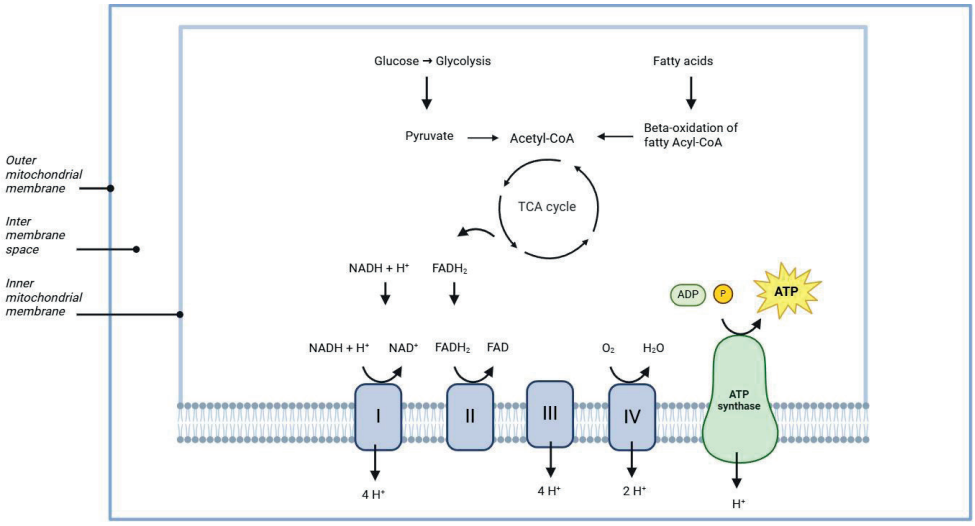
3. Mitochondrial (dys)function in health and critical illness

3.1 Mitochondrial function and homeostasis in health

The primary function of mitochondria, also known as cell powerhouses, is to produce most of the energy required for cellular functioning in a process called oxidative phosphorylation (34,35). Typically, acetyl coenzyme A (Acetyl-CoA, derived from glycolysis of carbohydrates as pyruvate and the beta-oxidation of fatty acids) is oxidised in the Tricarboxylic Acid Cycle (TCA) to carbon dioxide and water. In this process, hydrogen ions are generated, reducing nicotinamide-adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) to NADH and $FADH_2$, respectively (**Figure 1**).

Subsequently, NADH and $FADH_2$ provide electrons to the mitochondrial electron transport chain (ETC) at the inner mitochondrial membrane, composed of five protein complexes (complexes I-V) and several electron transporters. The movement of electrons across the ETC results in an electrochemical gradient, which is used to phosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) via the ATP-synthase (also known as complex V) (29,34-36). In this last step, oxygen is reduced to water.

Figure 1. Schematic overview of ATP production in a mitochondrion via the process of oxidative phosphorylation



Acetyl-CoA = acetyl coenzyme A; ADP = adenosine diphosphate; ATP = adenosine triphosphate; $FADH_2$ = flavin adenine dinucleotide (FAD) + 2 hydrogen ions (H_2); H^+ = hydrogen ion; H_2O = dihydrogen oxide ("water"); NADH = nicotinamide-adenine dinucleotide (NAD) + 1 hydrogen ion (H^+); O_2 = dioxygen ("oxygen"); P = inorganic phosphate; TCA = tricarboxylic acid cycle. Created with Biorender.com for this thesis.

Of note, the ETC is not 100% efficient (34,37). Approximately 98-99% of the oxygen the mitochondria consume is used for ATP production (the so-called "coupled respiration"). However, a small amount is used for "uncoupled respiration", a process in which the gradient across the ETC is not coupled with oxidative phosphorylation and ATP production. The incomplete reduction of water results in the production of reactive oxygen species (ROS). Typically, mitochondria protect themselves from damage induced by (these) ROS via several antioxidants, such as glutathione (34,38). However, when large amounts of ROS are generated, these systems may become overwhelmed. Interestingly, coupled and uncoupled respiration ratios vary between tissues: between 85% in heart tissue and up to 50% in skeletal muscle (35,37,39).

In addition to ATP generation, mitochondria are essential for other cellular functions, such as calcium homeostasis and immunity (36). Moreover, they play a crucial role in

metabolic stress situations. For instance, in hypoxic conditions, the production of ROS is increased, affecting vascular tone and angiogenesis. Mitochondria ultimately contribute to autophagy and apoptosis, the processes essential to clearing cellular damage (35,40).

Mitochondrial repair mechanisms

Damaged and discarded mitochondria are replaced in a process called mitochondrial biogenesis. In addition, mitochondria usually undergo continuous cycles of fusion and fission, allowing the exchange of damaged components (fusion). Subsequently, the newly fused mitochondrion splits into two new mitochondria (fission), thereby diluting the damage or concentrating it into one dysfunctional mitochondrion, which is targeted for mitochondrial autophagy (mitophagy) (5,41). Under normal conditions, the processes of mitochondrial biogenesis, fusion, fission, and autophagy are nicely balanced.

3.2 Mitochondrial function in critical illness

As mentioned above, general mitochondrial dysfunction was observed during the early stages of sepsis (30). During the body's systemic inflammatory response to infection, there is an increased demand for energy production in the form of ATP. However, hypoxemia, hyperglycemia (amongst others due to insulin resistance) and the production of nitric oxide and other ROS damage mitochondria directly and inhibit the ETC, resulting in uncoupling of the process of oxidative phosphorylation (5,35,41). Damage to the mitochondrial membrane causes the release of proapoptotic factors into the cytosol and leakage of mitochondrial content such as mitochondrial deoxyribonucleic acid (DNA) (39,42). This mitochondrial content, in turn, serves as danger-associated molecular patterns (DAMPs), aggravating the inflammatory response. Concomitantly, the production of mitochondrial proteins to restore damage (mitochondrial biogenesis) is downregulated (34). These pathophysiological processes result in a vicious cycle of decreased ATP production, accumulation of ADP and lactate, and augmented production of ROS. This mitochondrial dysfunction is associated with unfavourable clinical outcomes. Brealy *et al.* demonstrated that the absolute muscle ATP concentrations and ATP:ADP ratios were significantly lower in non-survivors (29).

Bio-energetic downregulation

Cell death pathways would be activated when cell metabolism continues at the same state in this ATP-insufficient environment (34). Interestingly, several studies have shown that sepsis and multiple organ failure are accompanied by only minimal signs of histologic structural damage to the organs themselves (35,38,43). Moreover, organs can recover within days to weeks, including those with poor regenerative capacity (34,35,37). Therefore, mitochondria are thought to enter a metabolic downregulation

("hibernation") state to cope with this failing energy supply and decrease metabolic demands to preserve cell life (34,38,41).

However, limited studies investigate the progression of mitochondrial function and dynamics during the early and late acute phases of sepsis. More knowledge of the hypermetabolic inflammatory state, mitochondrial function and dynamics and clinical outcomes in septic ICU patients will improve the theoretical base for treatment strategies, such as insulin therapy or the timing of (par)enteral nutrition (25). Therefore, **Chapter 7** aims to better understand of the progress of mitochondrial (dys)function during the initial and late acute phases of sepsis in ICU patients. We hypothesised that the degree of mitochondrial dysfunction is associated with the degree of inflammation, the sepsis-related organ failure assessment score (Sequential organ failure assessment score (SOFA)) and mortality.

Theoretically, this sepsis-induced bioenergetic downregulation may be worsened by iatrogenic mitochondrial dysfunction, aggravating multiple organ failure and thus influencing clinical outcomes, but this has not been studied extensively yet. For instance, experimental in vitro studies have shown that propofol – a frequently used sedative drug used in patients requiring mechanical ventilation – may harm mitochondrial function by disturbing free fatty acid oxidation and interfering with the activity of the electron transport chain complexes (44,45). However, the long-term effects of propofol for prolonged sedation in critically ill patients have not been studied well. In **Chapter 8** we hypothesised that the effect of propofol on mitochondria negatively impacts clinical outcomes, such as mortality and ICU-AW (and thus the need for a tracheostomy to wean from mechanical ventilation). Furthermore, it could potentially affect the discharge destination, as patients with ICU-AW are more likely to be discharged to rehabilitation centres or nursing homes.

Persistent muscle weakness in the post-acute phase

As described above, patients may suffer from prolonged ICU-AW symptoms in the post-ICU convalescence, indicated by sustained ICU-AW (part of PICS). Again, the underlying pathophysiology needs to be better understood. It is likely multifactorial with (prolonged) mitochondrial dysfunction playing a pivotal role, as demonstrated by Jiroutkova *et al.* (24). They observed a 50% reduction in the capacity to generate ATP in the quadriceps muscles of patients with a protracted critical illness. Similar results are reported by Owen and co-workers, who observed morphological abnormalities in skeletal muscle mitochondria from sepsis-surviving mice. Two weeks post-sepsis, the mitochondria showed a persistent decreased capacity for oxidative phosphorylation (46).

Recently, there has been emerging interest in the repair mechanisms of mitochondria in the long term. The hypothesis is that survival from critical illness requires sufficient activation of these repair mechanisms to prevent ongoing mitochondrial dysfunction, which may negatively influence clinical outcomes. As such, Carré and colleagues demonstrated that early activation of restorative mitochondrial biogenesis in vastus lateralis muscle biopsies was associated with survival (47). In addition, Vanhorebeek *et al.* observed insufficient autophagy in the liver and skeletal muscle of critically ill patients (48). In similar animal studies, markers of insufficient autophagy were more elevated in non-surviving animals than in those who survived (49). Other studies investigated the role of muscle stem (satellite) cells. Dos Santos *et al.* observed that the mechanisms involved in muscle wasting in the acute phase of illness (such as proteolysis and inflammation) normalised at six months post-ICU discharge, but muscle regeneration did not correlate with the resolution of muscle weakness. They found that the content of muscle stem (satellite) cells was decreased at six months post-discharge, suggesting that impairment of these cells plays a role in poor muscle regeneration and sustained weaknesses (50). Similar findings were reported by Rocheteau and co-workers who observed a massive loss of stem cells during the acute phase of sepsis. The remaining stem cells showed abnormal mitochondrial activity (51). However, further research is warranted to elucidate the exact pathophysiology of these deficient repair mechanisms and find targets for therapy.

4. Strategies to reduce ICU-AW and PICS

There are minimal evidence-based therapies to combat ICU-AW and PICS, optimising QoL in the post-ICU convalescence (5,6). Current strategies mainly focus on diminishing the risk factors, such as proper management of hyperglycemias and shortening the duration of mechanical ventilation (6). Pandharipande and co-workers proposed five evidence-based steps to improve care and long-term outcomes of mechanically ventilated patients, summarized in the ABCDE bundle. This abbreviation includes Awakening and Breathing Coordination of daily sedation and ventilator removal trials; Choice of sedative or analgesic exposure; Delirium monitoring and management; and Early Mobility and Exercise (52). Critically ill patients are often administered sedative-hypnotic and analgesic agents to optimise comfort, reduce pain, anxiety and stress, and facilitate patient-ventilator synchrony (52,53). However, these sedatives are (indirectly) associated with morbidity, such as ICU-AW, as these possibly augment muscle wasting by altering the response of excitatory neurotransmitters, hampering early mobilisation and increasing the risk of delirium (7,52,54). The 'ABC' in the ABCDE bundle is used to combat this. Girard and colleagues demonstrated in the Awakening and Breathing Controlled trial that 168 patients who received daily paired spontaneous awakening

and spontaneous breathing trials had more ventilator-free days (14.7 (SD 0.9) versus 11.6 (SD 0.9)), shorter ICU and hospital lengths of stay (about four days), and lower all-cause one-year mortality (hazard ratio (HR) 0.68, 95% confidence interval (95% CI) 0.50-0.92; p = 0.01) compared to those who received standard of care (55). Moreover, fewer patients from the intervention group needed a tracheostomy to wean from mechanical ventilation (13% versus 20%), although this difference was not statistically significant. Therefore, daily interruption of sedatives and spontaneous breathing trials are recommended whenever possible to improve the patient's clinical outcomes.

For the second component of the ABCDE bundle (the 'D'), easy-to-use delirium monitoring scores have been developed. Several studies have demonstrated the adverse effects of delirium on mid- and long-term clinical outcomes, such as increased impaired cognitive functioning, increased likelihood of being discharged to a rehabilitation centre and increased one-year mortality (56-59). Modifiable risk factors, and thus possible strategies for preventive measures in the ICU, include early correction of hypoxia and electrolyte-, metabolic- and sleep- disturbances. However, the most substantial predisposing risk factor for delirium is administered drugs, particularly benzodiazepines. Therefore, unnecessary use should be reduced (58,60).

Concerning the E' of the ABCDE bundle, early mobilisation and exercise are proposed. However, studies assessing the effect of early mobilisation on clinical outcomes are inconsistent and show that it does not improve long-term outcomes (28,46). The most recent systematic review and meta-analysis by Wang *et al.*, evaluating 60 trials of physical rehabilitation in critically ill patients, concluded that early physical rehabilitation only reduces the length of stay in the ICU and hospital and improves physical functioning at hospital discharge (61). No differences between the intervention and the control groups were observed regarding long-term outcomes, such as psychical functioning at six months post-ICU discharge and experienced QoL. These findings may indicate ongoing mechanisms hampering muscle function regain, Boelens *et al.* suggested. However, the results should be interpreted cautiously due to highly heterogeneous studies with a significant risk of bias (28).

Wischmeyer suggested expanding this bundle with F (Targeted feeding and early adequate protein) and G (Gain function and grow muscle) (2). Undoubtedly, the recovery of muscle mass and function after the acute phase of critical illness can only be accomplished with adequate energy and protein delivery. However, the disrupted metabolism during critical illness has consequences for nutrition therapy.

5. Understanding the relationship between disrupted metabolism and nutrition therapy

In the past, *nutritional support* in critically ill patients was regarded as exogenous fuel to preserve lean body mass and replace oral intake in those unable to eat (62). However, more recently, this strategy has evolved to *nutritional therapy*, in which nutrition helps to attenuate catabolism (and thus reduce muscle wasting) and maintain nutritional status to improve clinical outcomes (4). There is increasing evidence for time- and dose-dependent (and thus patient-targeted) nutrition – there is no "one size fits all" (4,63,64). Critically ill patients preferably receive nutritional support matching their metabolic needs in the ICU and post-ICU period. However, this is complex as patients' caloric and macronutrient (such as protein) requirements vary significantly throughout their ICU journey (2,35,64,65). To better guide nutrition in the several phases of critical illness, it has been proposed to categorise these phases into early acute (ICU days 1-2), late acute (days 3-7) and recovery (>7 days) phases. However, no clinical marker is currently known, indicating the transition from one phase to another (64,66,67). Nevertheless, the several phases of acute illness and their different phases of mitochondrial dysfunction and metabolic downregulation may affect nutritional support concerning clinical outcomes. Therefore, it is no wonder that feeding trials in critically ill patients show inconsistent and conflicting results.

Nutritional support in the different phases of critical illness

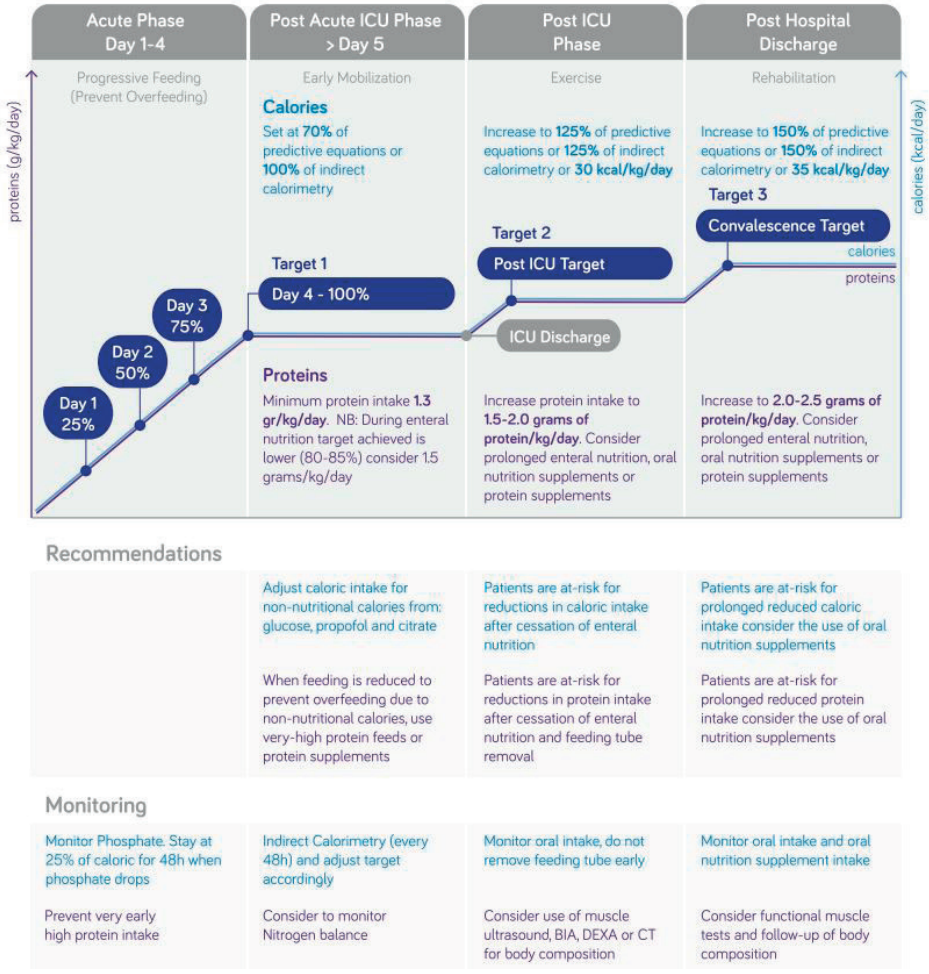
5.1 Right time…

As mentioned before, in the acute phase of critical illness, there is a significant increase in endogenous energy production and, at the same time, demands are lower as the body's metabolism is downregulated, probably as a protective mechanism against severe stress (hibernation-like state; bioenergetic downregulation). It is thought that mitochondria cannot utilise substrates in this phase, and early aggressive feeding will result in "nutritrauma" as demonstrated by several recent randomised controlled trials (41,68,69). Early full nutritional support in these trials was related to adverse clinical outcomes such as prolonged mechanical ventilation and increased mortality (39,70). Furthermore, higher protein delivery in this phase was associated with significantly more muscle loss (22). McKeever *et al.* demonstrated an increased oxidative burden in critically ill patients who achieved their estimated resting energy expenditure (REE) compared to patients who were fed at 40% of targets (42). On the contrary, Hermans and colleagues observed in subanalyses of the EPaNIC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients) trial that a significant macronutrient deficit during the first seven days of critical illness did not increase muscle wasting but resulted

in more efficient activation of autophagy as demonstrated in in-vivo skeletal muscle needle biopsies (71). As such, feeding may counteract this (39,49,70-73).

Conversely, in the chronic or recovery phase, patients' metabolic needs increase drastically (2,65). Therefore, a stepwise approach to providing calories and proteins during the several phases of critical illness is recommended, as proposed by Van Zanten *et al.* (see **Figure 2**)(74).

Figure 2. Stepwise approach to provide calories and proteins during the several phases of critical illness



BIA = bioelectrical impedance analysis; CT = computed tomography scanning; DEXA = dual-energy X-ray absorptiometry; ICU = Intensive care unit; g/kg/day = grams of proteins per kilogram per day; kcal/day = total kilocalories per day.
During the first 3 days, calories and proteins are gradually progressed in steps of +25% per day to the calculated target on day 4.
Reproduced with permission from (74).

5.2 …Right dose…

Accurate estimations of energy requirements are essential to guide nutritional therapy to prevent under- and overfeeding (67,75-77). Predictive equations – such as the Harris-Benedict equation - are commonly used in clinical settings to predict REE (78). However, predictive equations are population-based averages, have lower accuracy rates than indirect calorimetry, and are unreliable in predicting REE in individual patients (67,79). Therefore, the European Society for Clinical Nutrition and Metabolism (ESPEN) adult ICU guideline recommends indirect calorimetry to estimate REE during critical illness to determine individual ICU patients' energy requirements and guide optimal nutritional support (67). However, indirect calorimetry is not widely used as it is unavailable in many hospitals (80). Easy-to-use novel bedside systems may overcome this shortcoming, such as the Beacon Care system, designed as a continuous Intensive Care Clinical Advisory system for ventilated patients and equipped with an indirect calorimetry functionality (81). Its performance in determining REE compared with the current gold standard in our ICU will be studied in **Chapter 2**. Of note, nutritional support should be adapted to the amount of non-nutritional calories administered (such as trisodium citrate during renal replacement therapy and high-dose propofol) to prevent overfeeding. These may add up to one-third of the total daily calories in individual patients (82).

5.3 …Right macro- and micronutrients

5.3.1 Role of macronutrients

Many studies have focused on providing the right amount of energy at the right time. However, there is increasing evidence that macronutrient intake, especially adequate protein provision, is more important than cumulative energy intake, although randomised controlled trials are inconclusive (67,83-86).

Proteins

In this context, the adverse effects of full nutritional support in the early acute phase of critical illness on clinical outcomes, such as observed in the EPaNIC trial, may be due to the high intake of different macronutrients, particularly proteins and not to total caloric load per se (74,85). However, results from available studies about protein administration in critical illness are conflicting, probably due to heterogeneous study populations and – even more importantly – the assumed time-dependent effect of protein intake (83,85). As mentioned, Puthucheary and co-workers demonstrated more significant muscle loss in the patients who received higher protein doses during the first week of ICU admission (22). Koekkoek *et al.* observed increased mortality among patients with higher protein intake (defined as ≥0.8g/kg*day) during the early acute phase of ICU admission (days 1-2) in a retrospective cohort of 455 patients (83). Furthermore, reduced 6-month mortality rates were observed in the groups with low protein intake (≤0.8 g/kg*day) in

the first two days after ICU admission, intermediate (0.8-1.2 g/kg*day) during days 3-5 and subsequently high intake (≥1.2 g/kg*day), after adjustment for relevant covariates. Based on available studies and knowledge, the ESPEN guidelines recommend a gradual increase in protein administration to a target of 1.3 g/kg*day (67).

Carbohydrates

As mentioned in the section about *Mitochondrial function and homeostasis in health*, carbohydrates are the primary substrate for mitochondrial energy production. The ESPEN guideline recommends administering carbohydrates at a maximum of 5 mg/kg*min (67). However, due to the body's stress response in critical illness, endogenous glucose production increases dramatically and produces hyperglycemia with increased insulin resistance (67,87,88). These hyperglycemias are more profound in patients who receive early aggressive feeding than those who do not, as demonstrated in the EAT-ICU and TARGET trials (89,90). Severe hyperglycemias are associated with - amongst others - additional mitochondrial damage and altered lipid metabolism (87,91). Moreover, it has been associated with increased morbidity and mortality compared to patients on tight glycemic control (92,93). Therefore, an aggressive caloric intake in the first week of ICU admission is not recommended. Instead, a progressive increase in calorie delivery during the first three days to the final target is suggested, as proposed by Van Zanten *et al.* (74).

Lipids

Thirdly, critical illness is accompanied by a dysregulated lipid metabolism, including a deficient carnitine (necessary for the transfer of long fatty acids to mitochondria for subsequent beta-oxidation) status and an impaired beta-oxidation of free fatty acids (FFA) to Acetyl-CoA, an essential substrate for the tricarboxylic acid cycle (67,87,94,95). As a result, this reduction in the efficiency of beta-oxidation of FFA and other changes in lipid metabolism result in 1) reduced ATP production, and thus energy deficiency, and 2) accumulation of FFA and other lipid intermediates (lipotoxicity) causing direct harm to mitochondria (87). Therefore, the ESPEN guidelines recommend administering intravenous lipids at a maximum of 1.5 g/kg*day (including lipids derived from non-nutritional sources) to prevent lipid overload (67). Lipids contribute about 29% up to 50% of the total calories provided in (par)enteral nutrition. Puthucheary *et al.* studied the association between bioenergetic status, alterations in fat metabolism and skeletal muscle wasting during the early phase of critical illness, using vastus lateralis muscle biopsies from 63 intensive care patients. They observed that decreased ATP production and impaired fat oxidation resulting in lipid accumulation are directly associated with skeletal muscle wasting. However, the amount of (nutritional and non-nutritional) lipids administered was *un*related to ATP content and skeletal muscle mass and may thus be bioenergetically inert during the acute phase of critical illness (96).

5.3.2 Role of micronutrients

As mentioned before, mitochondria protect themselves from damage induced by ROS via the antioxidant system, which consists of several enzymes and non-enzymatic compounds, including various dietary vitamins and (trace) minerals, such as vitamins A, C and E, copper, manganese, selenium, and zinc (25,34,35,38,97,98). A detailed discussion about their role in mitochondrial functioning is beyond the scope of this introduction and can be found elsewhere (see references above).

Although knowledge about the role of micronutrients in critical illness is scarce and studies show conflicting results, deficiencies in these micronutrients may likely contribute to increased morbidity and mortality, as is known for vitamin D deficiency (98-101). Therefore, the ESPEN micronutrient guideline recommends supplementing all essential trace elements and vitamins (100).

6. Preventing adverse events from nutrition therapy

6.1 Safe tube feeding

Very often, critically ill patients admitted to an ICU cannot have oral intake as they are sedated and mechanically ventilated and should get enteral (EN) or parenteral (PN) nutrition. Early EN (i.e., within 48 hours of ICU admission) is preferred over PN by the European, American and Canadian guidelines on clinical nutrition in critically ill, with gastric access as the standard approach (62,67,102). Most nasogastric feeding tubes are inserted blindly, which can be challenging in patients with reduced consciousness and weakened cough reflexes and may lead to severe complications (103,104). Post-pyloric feeding should be considered in patients with a high risk of aspiration, proximal enteric fistulae, or in cases of persistent gastric feeding intolerance despite the administration of prokinetics (62,67). Nasojejunal feeding tubes to facilitate post-pyloric feeding are placed using a guided placement method, such as real-time electromagnetic signals (Cortrak) or with an endoscope by gastroenterologists. However, these guided procedures may significantly delay nutritional delivery due to the limited availability of qualified operators and equipment (105,106). Other disadvantages of endoscopic placement include the staffing costs (endoscopy team), distress and discomfort for the patient, sedation requirements, time-consuming appointments with different departments and – in some hospitals – the risk of transporting critically ill patients through the hospital. Newer bedside techniques using integrated real-time imaging technology are suggested as a better alternative since these enteral feeding tubes (either nasogastric or nasojejunal) are equipped with a mini video camera at the distal tip, allowing real-time visualisation of anatomic landmarks on an external portable monitor during tube insertion (107). The performance of this novel device is evaluated in **Chapter 3**.

We hypothesised that post-pyloric feeding tube placement using this technology is simple, safe and efficient in ICU patients, providing identification of the esophagus and stomach (and small intestines if desired) and guiding accurate placement.

6.2 Refeeding hypophosphatemia (RH) and refeeding syndrome (RFS)

Of note, the reintroduction of (par)enteral feeding after a period of fasting or starvation might induce refeeding syndrome (RFS) in patients at risk (108-112; as will be described in **Chapter 4**). RFS describes a spectrum of clinical symptoms resulting from biochemical abnormalities, typically fluid and electrolyte imbalances, with refeeding hypophosphatemia (RH) playing a central role. Additionally, abnormalities in glucose metabolism and vitamin (thiamine) deficiencies are frequently seen (110-114).

Pathophysiology of RFS

During prolonged fasting, our metabolism switches to fat and protein utilisation after depleting glycogen stores. Upon refeeding, especially carbohydrates, metabolism switches back to the breakdown of ingested carbohydrates. This response results in a marked increase in insulin secretion, increasing intracellular glucose uptake and electrolytes such as phosphate, potassium, and magnesium (110,113). This shift and depleted electrolyte storage may lead to low electrolyte concentrations (115). Simultaneously, insulin resistance is observed – marked by the coexistence of hyperinsulinemia and hyperglycemia – resulting in increased sodium and water retention, most likely due to an anti-natriuretic effect of insulin on the renal tubules. This effect may result in extracellular volume expansion, leading to peripheral oedema and – if severe enough – to heart failure and pulmonary oedema (110,113,115,116). Transcellular shifts and redistributions of electrolytes may result in cardiac (arrhythmia), neuromuscular (muscle weakness, spasms, rhabdomyolysis) and hematopoietic (anaemia and reduced oxygen supply) impairment. This pathophysiology altogether may result in organ dysfunction, (multiple) organ failure and ultimately death if not appropriately treated (108,113,114,116-118).

Identification and diagnosis of RH

Due to several definitions using electrolyte disturbances with different cut-off values and/or clinical symptoms, the incidence of RFS remains unknown in critically ill and non-critically ill patients. In a systematic review by Friedli and co-workers, eleven of 32 studies reported an incidence of zero percent (116). Narrow definitions of RFS and heterogeneous patient groups may have caused this. Other studies using broader definitions reported RFS incidences up to 80%, mainly occurring in the first 72 hours after the start of nutritional support (116). In critically ill patients, refeeding syndrome is most often defined by new onset hypophosphatemia (refeeding hypophosphatemia, RH) with a fall of serum phosphate levels of >0.16 mmol/L to below 0.65 mmol/L within 72

hours of the initiation of feeding, not attributable to other causes. Using this definition, the incidence of RH is reported to be around 35% in critically ill patients (119,108).

Treatment of RH in the ICU

Standard treatment for RH consists of strict monitoring of the patient, supplementation of electrolytes and vitamins (particularly thiamine/vitamin B1), and, if necessary, fluid correction and insulin therapy (108,111,112,117,118). There has been considerable debate about energy intake during this period; recommendations vary between a full caloric strategy, restricted intake and immediate discontinuation of nutritional therapy (108-111,114,116,118,120). A reduction in 6-month mortality has been demonstrated in patients with RH who received hypocaloric (<50% of calculated targets) feeding compared to patients who received normocaloric feeding (adjusted HR 0.39, 95% CI 0.16-0.95%, p = 0.037) (108). Similar findings were reported by Doig and co-workers, who demonstrated a 90-day survival benefit in patients receiving caloric restriction (<500 kcal/day) after the onset of RH (120). Based on these observations, the ESPEN guidelines recommend restricting caloric intake for 48 hours (67). However, in current guidelines and literature, most attention is paid to the provision of calories, but not to individual macronutrients (such as proteins), as the pathophysiology of RFS is considered to be related to carbohydrate intake (see the section about pathophysiology above) (25,84,121).

Nevertheless, there is increasing evidence that macronutrient intake, especially adequate and careful protein provision, is more important than cumulative energy intake, as described in section 5.3 (83-86,122). Whether this is true for patients with RH is also studied in **Chapter 5**. We hypothesised that RH patients with lower protein intake (defined as ≤0.71 g/kg*day) during the early acute phase of ICU admission (days 1-3) have a survival benefit compared to RH patients with a higher protein intake.

7. Optimising post-ICU nutrition – strategies to improve long-term outcomes

As stated above, patients' metabolic targets and physical mobility increase significantly during the recovery phase of critical illness and in the post-ICU hospitalisation period (63,65, 74,123). Their energy expenditure exceeds the guideline-recommended energy and protein intake in this period (65). Simultaneously, patients are expected to return to oral nutrition gradually, a transition phase in which they are prone to accumulate energy and protein deficits, which may result in suboptimal recovery (4,124,125).

Although much research has been done during ICU stay, detailed information about nutritional intake during the post-ICU hospitalisation period in general wards is lacking – and so are formal guidelines about individualized nutritional support to close the nutritional gap in this convalescence phase. Available literature assessing nutritional performance in the post-ICU period in general wards is scarce, based on studies with small sample sizes and no daily nutritional assessment (126).

Ridley *et al.* conducted a nested cohort study within a randomised controlled trial, comparing supplemental PN with standard care, studying the nutritional intake of 32 patients in the post-ICU hospitalisation period (124). They reported median overall energy and protein adequacies of 79% and 73%, respectively. Importantly, adequacy was highly dependent on patients' nutritional route. Patients with oral nutrition only had the lowest intake; they only met up to 66% and 60% of prescribed energy and protein targets. Notably, these patients received food fortification (energy and/or protein-enriched) and/or oral nutritional supplements. When no oral supplements were provided, energy and protein adequacies were notably worse: 37% and 48%, respectively. On the contrary, energy (104%) and protein (99%) adequacies were the highest in patients with combined oral and enteral nutrition (124). In addition to these findings, we will provide a complete representation of the energy and protein intake over the entire post-ICU hospitalization period in **Chapter 6**, based on daily intake measurements and also describing the period around the discontinuation of enteral nutrition.

Of note, the exact etiology for this inadequate intake in the post-ICU period is not clearly understood yet, but it is likely multifactorial. Patient factors such as a change in taste, appetite and satiety, reduced physical (including swallowing) function, gastrointestinal intolerance (including nausea), and psychological factors (such as delirium and depression) play a role (125,127-129). Last but not least, several clinical management and system factors may compromise nutritional intake in this period as well, often arising from knowledge deficits, such as the lack of a precise nutrition plan in the transfer documentation to the ward, premature enteral feeding tube removal, competing work priorities (including less time for feeding assistance and support), and the absence of on-demand room service resulting in rigid meal times and structures (123,125,130-132).

It is unknown whether nutritional intake in the post-ICU hospitalisation period is associated with clinical outcomes, such as length of hospital stay, morbidity and mortality. However, in a multicenter trial outside critical care, it has been demonstrated that individualized nutritional support increases energy and protein intake and lowers the risk of 30-day adverse outcomes and mortality (125,133). Based on these results, it

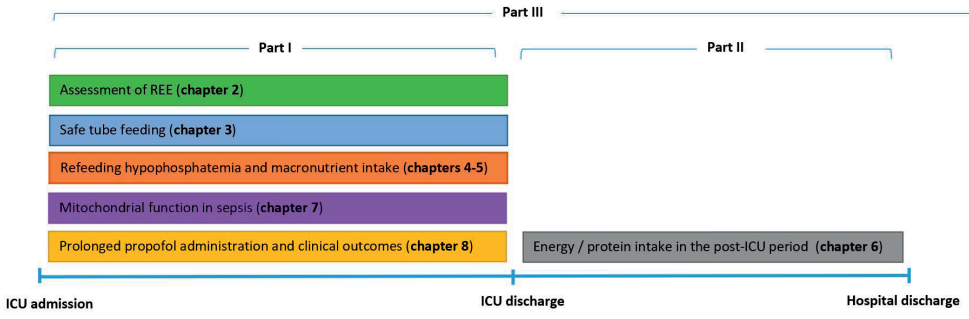
is likely that nutritional interventions in the post-ICU period may also impact recovery and clinical outcomes (125). Optimising protein and energy intake might be essential to attenuate further loss of lean body mass and promote restoration of physical functioning and QoL (63,74,123). In **Chapter 6**, we will investigate the association between reached nutritional targets and clinical endpoints, such as length of hospital stay after ICU discharge, discharge destinations, readmission, and mortality rates. We hypothesised that adequate nutrition in the post-ICU period may positively impact clinical outcomes.

8. Outline of this thesis

This thesis aims to increase knowledge on an essential part of treating critically ill patients: nutrition, with particular attention to disrupted metabolism. As described above, there is a growing need for patient-targeted strategies to optimise nutritional therapy in the ICU and convalescence to improve long-term outcomes and QoL of ICU survivors.

This thesis is divided into three parts: nutrition in the ICU (part 1) and post-ICU period (part 2) and the possible metabolic interactions of continuous sedation with an effect on long-term outcomes (part 3). See also **Figure 3**.

Figure 3. Thesis outline



ICU = intensive care unit; REE = resting energy expenditure.

8.1 Part 1: Nutrition in the ICU

Chapter 2 a novel indirect calorimeter is compared to the current gold standard in determining resting energy expenditure (REE) in mechanically ventilated ICU patients. In addition, measured REE is compared to calculated REE by predictive equations. **Chapter 3** investigates the performance of video-assisted post-pyloric feeding tube

placement using a novel feeding tube with Integrated Real-Time Imaging System (IRIS-) technology. **Chapter 4** reviews current literature to provide an overview of recent findings concerning refeeding hypophosphatemia (RH) in critically ill patients, including recommendations for daily practice. Finally, **Chapter 5** investigates the effect of macronutrient intake of patients with RH during the first week of ICU admission on clinical outcomes.

8.2 Part 2: Nutrition in the post-ICU period

Part 2 of this thesis considers in detail energy and protein intake over the post-ICU hospitalisation period and explores associations between protein intake and clinical outcomes (**Chapter 6**).

8.3 Part 3: (Progression of) mitochondrial function in critical illness

Chapter 7 studies the evolution and resolution of mitochondrial (dys)function in peripheral blood mononuclear cells during the early phase of sepsis in ICU patients. Finally, **Chapter 8** investigates the association between prolonged administration of the frequently used sedative drug propofol and clinical outcomes.

Finally, **Chapter 9** provides a general discussion of the main conclusions of the current work, including clinical implications and future research directions.

References

1. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012 Feb;40(2):502-9.
2. Wischmeyer PE. Are we creating survivors…or victims in critical care? Delivering targeted nutrition to improve outcomes. Curr Opin Crit Care. 2016 Aug;22(4):279-84.
3. Oshima T, Deutz NE, Doig G, Wischmeyer PE, Pichard C. Protein-energy nutrition in the ICU is the power couple: A hypothesis forming analysis. Clin Nutr. 2016 Aug;35(4):968-74.
4. Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW; Enhanced Recovery After Critical Illness Programme Group (ERACIP) investigators. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017 Aug 26;21(1):226.
5. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. Physiol Rev. 2015 Jul;95(3):1025-109.
6. Lad H, Saumur TM, Herridge MS, Dos Santos CC, Mathur S, Batt J, et al. Intensive care unit-Acquired Weakness: Not just Another Muscle Atrophying Condition. Int J Mol Sci. 2020 Oct 22;21(21):7840.
7. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med. 2020 Apr;46(4):637-653.
8. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011 Oct;10(10):931-41.
9. Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med. 2009 Oct;37(10 Suppl):S299-308.
10. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med. 2014 Dec 15;190(12):1437-46.
11. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, et al. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med. 2017 Sep;43(9):1270-1281.
12. Geense WW, Zegers M, Peters MAA, Ewalds E, Simons KS, Vermeulen H, et al. New Physical, Mental, and Cognitive Problems 1 Year after ICU Admission: A Prospective Multicenter Study. Am J Respir Crit Care Med. 2021 Jun 15;203(12):1512-1521.
13. Colbenson GA, Johnson A, Wilson ME. Post-intensive care syndrome: impact, prevention, and management. Breathe (Sheff). 2019 Jun;15(2):98-101.
14. Harvey MA, Davidson JE. Postintensive Care Syndrome: Right Care, Right Now…and Later. Crit Care Med. 2016 Feb;44(2):381-5.
15. Meyer-Frießem CH, Malewicz NM, Rath S, Ebel M, Kaisler M, Tegenthoff M, et al. Incidence, Time Course and Influence on Quality of Life of Intensive care unit-Acquired Weakness Symptoms in Long-Term Intensive Care Survivors. J Intensive Care Med. 2021 Nov;36(11):1313-1322.
16. Griffiths J, Hatch RA, Bishop J, Morgan K, Jenkinson C, Cuthbertson BH, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care. 2013 May 28;17(3):R100.

17. Dowdy DW, Eid MP, Sedrakyan A, Mendez-Tellez PA, Pronovost PJ, Herridge MS, et al. Quality of life in adult survivors of critical illness: a systematic review of the literature. Intensive Care Med. 2005 May;31(5):611-20.
18. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011 Apr 7;364(14):1293-304.
19. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med. 2009 Apr;41(5):360-6.
20. Hua M, Gong MN, Brady J, Wunsch H. Early and late unplanned rehospitalisations for survivors of critical illness. Crit Care Med. 2015 Feb;43(2):430-8.
21. Flower L, Puthucheary Z. Muscle wasting in the critically ill patient: how to minimise subsequent disability. Br J Hosp Med. 2020 Apr 2;81(4):1-9.
22. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013 Oct 16;310(15):1591-600.
23. Pfoh ER, Wozniak AW, Colantuoni E, Dinglas VD, Mendez-Tellez PA, Shanholtz C, et al. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. Intensive Care Med. 2016 Oct;42(10):1557-1566.
24. Jiroutková K, Krajčová A, Ziak J, Fric M, Waldauf P, Džupa V, et al. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. Crit Care. 2015 Dec 24;19:448.
25. Preiser JC, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015 Jan 29;19(1):35.
26. Klaude M, Mori M, Tjäder I, Gustafsson T, Wernerman J, Rooyackers O. Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. Clin Sci. 2012 Feb;122(3):133-42.
27. Fredriksson K, Tjäder I, Keller P, Petrovic N, Ahlman B, Schéele C, et al. Dysregulation of mitochondrial dynamics and the muscle transcriptome in ICU patients suffering from sepsis induced multiple organ failure. PloS one. 2008;3(11):e3686.
28. Boelens YFN, Melchers M, van Zanten ARH. Poor physical recovery after critical illness: incidence, features, risk factors, pathophysiology, and evidence-based therapies. Curr Opin Crit Care. 2022 Aug 1;28(4):409-416.
29. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002 Jul 20;360(9328):219-23.
30. Garrabou G, Morén C, López S, Tobías E, Cardellach F, Miró O, et al. The effects of sepsis on mitochondria. J Infect Dis. 2012 Feb 1;205(3):392-400.
31. Japiassú AM, Santiago AP, d'Avila JC, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, et al. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity. Crit Care Med. 2011 May;39(5):1056-63.
32. Fredriksson K, Hammarqvist F, Strigård K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. Am J Physiol Endocrinol Metab. 2006 Nov;291(5):E1044-50.

33. Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. Crit Care. 2015;19 Suppl 3(Suppl 3):S6.
34. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence. 2014 Jan 1;5(1):66-72.
35. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. Biochim Biophys Acta Mol Basis Dis. 2017 Oct;1863(10 Pt B):2534-2545.
36. Supinski GS, Schroder EA, Callahan LA. Mitochondria and Critical Illness. Chest. 2020 Feb;157(2):310-322.
37. Singer M. Critical illness and flat batteries. Crit Care. 2017 Dec 28;21(Suppl 3):309.
38. Brealey D, Karyampudi S, Jacques TS, Novelli M, Stidwill R, Taylor V, et al. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. Am J Physiol Regul Integr Comp Physiol. 2004 Mar;286(3):R491-7.
39. McKeever L, Bonini M, Braunschweig C. Feeding During Phases of Altered Mitochondrial Activity: A Theory. JPEN J Parenter Enteral Nutr. 2018 Jul;42(5):855-863.
40. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012 Mar 16;148(6):1145-59.
41. McClave SA, Wischmeyer PE, Miller KR, van Zanten ARH. Mitochondrial Dysfunction in Critical Illness: Implications for Nutritional Therapy. Curr Nutr Rep. 2019 Dec;8(4):363-373.
42. McKeever L, Peterson SJ, Cienfuegos S, Rizzie J, Lateef O, Freels S, et al. Real-Time Energy Exposure Is Associated With Increased Oxidative Stress Among Feeding-Tolerant Critically Ill Patients: Results From the FEDOX Trial. JPEN J Parenter Enteral Nutr. 2020 Nov;44(8):1484-1491.
43. Kozlov AV, Bahrami S, Calzia E, Dungel P, Gille L, Kuznetsov AV, et al. Mitochondrial dysfunction and biogenesis: do ICU patients die from mitochondrial failure? Ann Intensive Care. 2011 Sep 26;1(1):41.
44. Krajčová A, Løvsletten NG, Waldauf P, Frič V, Elkalaf M, Urban T, et al. Effects of Propofol on Cellular Bioenergetics in Human Skeletal Muscle Cells. Crit Care Med. 2018 Mar;46(3):e206-e212.
45. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. Br J Anaesth. 2019 Apr;122(4):448-459.
46. Owen AM, Patel SP, Smith JD, Balasuriya BK, Mori SF, Hawk GS, et al. Chronic muscle weakness and mitochondrial dysfunction in the absence of sustained atrophy in a preclinical sepsis model. Elife. 2019 Dec 3;8:e49920.
47. Carré JE, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med. 2010 Sep 15;182(6):745-51.
48. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Güiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. 2011 Apr;96(4):E633-45.
49. Gunst J, Derese I, Aertgeerts A, Ververs EJ, Wauters A, Van den Berghe G, et al. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. Crit Care Med. 2013 Jan;41(1):182-94.
50. Dos Santos C, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive care unit Stay. A Pilot Study. Am J Respir Crit Care Med. 2016 Oct 1;194(7):821-830.

51. Rocheteau P, Chatre L, Briand D, Mebarki M, Jouvion G, Bardon J, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun. 2015 Dec 15;6:10145.
52. Pandharipande P, Banerjee A, McGrane S, Ely EW. Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Crit Care. 2010;14(3):157.
53. Devlin JW, Roberts RJ. Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. Anesthesiol Clin. 2011 Dec;29(4):567-85.
54. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extrem Physiol Med. 2015 Oct 9;4:16.
55. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008 Jan 12;371(9607):126-34.
56. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med. 2009 Dec 1;180(11):1092-7.
57. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. Neuropsychol Rev. 2004 Jun;14(2):87-98.
58. Pun BT, Ely EW. The importance of diagnosing and managing ICU delirium. Chest. 2007 Aug;132(2):624-36.
59. Zipser CM, Spiller TR, Hildenbrand FF, Seiler A, Ernst J, von Känel R, et al. Discharge Destinations of Delirious Patients: Findings From a Prospective Cohort Study of 27,026 Patients From a Large Health Care System. J Am Med Dir Assoc. 2022 Aug;23(8):1322-1327.e2.
60. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006 Jan;104(1):21-6.
61. Wang YT, Lang JK, Haines KJ, Skinner EH, Haines TP. Physical Rehabilitation in the ICU: A Systematic Review and Meta-Analysis. Crit Care Med. 2022 Mar 1;50(3):375-388.
62. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211.
63. Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. Crit Care. 2017 Dec 28;21(Suppl 3):316.
64. Lambell KJ, Tatucu-Babet OA, Chapple LA, Gantner D, Ridley EJ. Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care. 2020 Feb 4;24(1):35.
65. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. Crit Care Med. 1999 Jul;27(7):1295-302.
66. Cuthbertson DP, Angeles Valero Zanuy MA, León Sanz ML. Post-shock metabolic response. 1942. Nutr Hosp. 2001 Sep-Oct;16(5):176-82; discussion 175-6.
67. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019 Feb;38(1):48-79.
68. Yébenes JC, Campins L, Martínez de Lagran I, Bordeje L, Lorencio C, Grau T, et al. Nutritrauma: A Key Concept for Minimising the Harmful Effects of the Administration of Medical Nutrition Therapy. Nutrients. 2019 Aug 1;11(8):1775.

69. Moonen HPFX, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: consequences for nutrition therapy. Curr Opin Crit Care. 2020 Aug;26(4):346-354.
70. Van Dyck L, Casaer MP, Gunst J. Autophagy and Its Implications Against Early Full Nutrition Support in Critical Illness. Nutr Clin Pract. 2018 Jun;33(3):339-347.
71. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013 Oct;1(8):621-629.
72. Cuervo AM, Macian F. Autophagy, nutrition and immunology. Mol Aspects Med. 2012 Feb;33(1):2-13.
73. Derde S, Vanhorebeek I, Güiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology. 2012 May;153(5):2267-76.
74. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care. 2019 Nov 21;23(1):368.
75. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014 Dec 14;18(6):701.
76. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016 Nov 10;20(1):367.
77. Segadilha NLAL, Rocha EEM, Tanaka LMS, Gomes KLP, Espinoza REA, Peres WAF. Energy Expenditure in Critically Ill Elderly Patients: Indirect Calorimetry vs Predictive Equations. JPEN J Parenter Enteral Nutr. 2017 Jul;41(5):776-784.
78. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. Proc Natl Acad Sci U S A. 1918 Dec;4(12):370-3.
79. Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: A retrospective validation. Clin Nutr. 2019 Jun;38(3):1206-1210.
80. De Waele E, Spapen H, Honoré PM, Mattens S, Van Gorp V, Diltoer M, et al. Introducing a new generation indirect calorimeter for estimating energy requirements in adult intensive care unit patients: feasibility, practical considerations, and comparison with a mathematical equation. J Crit Care. 2013 Oct;28(5):884.e1-6.
81. Mermaid Care. Beacon Caresystem: Advisory system for ICU Ventilation and Nutrition [internet]. Available from: http://beaconcaresystem.com/beacon-caresystem/_[Accessed February 27, 2023].
82. Bousie E, van Blokland D, Lammers HJ, van Zanten AR. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr. 2016 Dec;70(12):1443-1450.
83. Koekkoek WACK, van Setten CHC, Olthof LE, Kars JCNH, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study. Clin Nutr. 2019 Apr;38(2):883-890.
84. Weijs PJ, Wischmeyer PE. Optimizing energy and protein balance in the ICU. Curr Opin Clin Nutr Metab Care. 2013 Mar;16(2):194-201.
85. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med. 2013 Feb 1;187(3):247-55.

86. van Zanten AR. Should We Increase Protein Delivery During Critical Illness? JPEN J Parenter Enteral Nutr. 2016 Aug;40(6):756-62.
87. Wasyluk W, Zwolak A. Metabolic Alterations in Sepsis. J Clin Med. 2021 May 29;10(11):2412.
88. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med. 2004 May;30(5):748-56.
89. Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R, et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med. 2017 Nov;43(11):1637-1647.
90. Chapman M, Peake SL, Bellomo R, Davies A, Deane A, Horowitz M, et al; TARGET Investigators, for the ANZICS Clinical Trials Group. Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. N Engl J Med. 2018 Nov 8;379(19):1823-1834.
91. Gunst J, Van den Berghe G. Blood glucose control in the ICU: don't throw out the baby with the bathwater! Intensive Care Med. 2016 Sep;42(9):1478-81.
92. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67.
93. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003 Feb;31(2):359-66.
94. Green P, Theilla M, Singer P. Lipid metabolism in critical illness. Curr Opin Clin Nutr Metab Care. 2016 Mar;19(2):111-5.
95. Barker G, Leeuwenburgh C, Brusko T, Moldawer L, Reddy ST, Guirgis FW. Lipid and Lipoprotein Dysregulation in Sepsis: Clinical and Mechanistic Insights into Chronic Critical Illness. J Clin Med. 2021 Apr 14;10(8):1693.
96. Puthucheary ZA, Astin R, Mcphail MJW, Saeed S, Pasha Y, Bear DE, et al. Metabolic phenotype of skeletal muscle in early critical illness. Thorax. 2018 Oct;73(10):926-935.
97. Koekkoek WA, van Zanten AR. Antioxidant Vitamins and Trace Elements in Critical Illness. Nutr Clin Pract. 2016 Aug;31(4):457-74.
98. Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr. 2019 Jun;38(3):982-995.
99. Casaer MP, Bellomo R. Micronutrient deficiency in critical illness: an invisible foe? Intensive Care Med. 2019 Aug;45(8):1136-1139.
100. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. Clin Nutr. 2022 Jun;41(6):1357-1424.
101. Amrein K, Papinutti A, Mathew E, Vila G, Parekh D. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. Endocr Connect. 2018 Dec 1;7(12):R304-R315.
102. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003 Sep-Oct;27(5):355-73.
103. Sparks DA, Chase DM, Coughlin LM, Perry E. Pulmonary complications of 9931 narrow-bore nasoenteric tubes during blind placement: a critical review. JPEN J Parenter Enteral Nutr. 2011 Sep;35(5):625-9.
104. Halloran O, Grecu B, Sinha A. Methods and complications of nasoenteral intubation. JPEN J Parenter Enteral Nutr. 2011 Jan;35(1):61-6.

105. Gerritsen A, van der Poel MJ, de Rooij T, Molenaar IQ, Bergman JJ, Busch OR, et al. Systematic review on bedside electromagnetic-guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes. Gastrointest Endosc. 2015 Apr;81(4):836-47.
106. Holzinger U, Brunner R, Miehsler W, Herkner H, Kitzberger R, Fuhrmann V, et al. Jejunal tube placement in critically ill patients: A prospective, randomised trial comparing the endoscopic technique with the electromagnetically visualised method. Crit Care Med. 2011 Jan;39(1):73-7.
107. Cardinal Health. Kangaroo™ Feeding Tube with IRIS Technology [internet]. Available from: https://www.cardinalhealth.com/en/product-solutions/medical/enteral-feeding/kangaroo-feeding-tube-with-iris-technology.html [Accessed February 28, 2023].
108. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clin Nutr. 2018 Oct;37(5):1609-1617.
109. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013 Jan 11;3(1):e002173.
110. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008 Jun 28;336(7659):1495-8.
111. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. Nutr Clin Pract. 2005 Dec;20(6):625-33.
112. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001 Jul-Aug;17(7-8):632-7.
113. Obeid OA, Hachem DH, Ayoub JJ. Refeeding and metabolic syndromes: two sides of the same coin. Nutr Diabetes. 2014 Jun 30;4(6):e120.
114. Fuentes E, Yeh DD, Quraishi SA, Johnson EA, Kaafarani H, Lee J, et al. Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive care unit. Nutr Clin Pract. 2017 Apr;32(2):252-257.
115. McCray S, Walker S, Parrish CR. Much ado about refeeding. Pract. Gastroenterol. 2004;28(12):26-44.
116. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: Results of a systematic review. Nutrition. 2017 Mar;35:151-160.
117. Boot R, Koekkoek KWAC, van Zanten ARH. Refeeding syndrome: relevance for the critically ill patient. Curr Opin Crit Care. 2018 Aug;24(4):235-240.
118. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008 Jun;62(6):687-94.
119. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg. 1996 Oct;131(10):1043-7.
120. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015 Dec;3(12):943-52.
121. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study. JPEN J Parenter Enteral Nutr. 2016 Jan;40(1):45-51.
122. Hoffer LJ. High-Protein Hypocaloric Nutrition for Non-Obese Critically Ill Patients. Nutr Clin Pract. 2018 Jun;33(3):325-32.

123. Obeid JN, Hodgson CL, Ridley EJ. Nutrition in the Post ICU Period: Where is the Evidence? ICU Manag & Pract. 2020;20(4):283-287.
124. Ridley EJ, Parke RL, Davies AR, Bailey M, Hodgson C, Deane AM, et al. What Happens to Nutrition Intake in the Post-Intensive care unit Hospitalization Period? An Observational Cohort Study in Critically Ill Adults. JPEN J Parenter Enteral Nutr. 2019 Jan;43(1):88-95.
125. Ridley EJ, Chapple LS, Chapman MJ. Nutrition intake in the post-ICU hospitalisation period. Curr Opin Clin Nutr Metab Care. 2020 Mar;23(2):111-115.
126. Slingerland-Boot R, van der Heijden I, Schouten N, Driessen L, Meijer S, Mensink M, et al. Prospective observational cohort study of reached protein and energy targets in general wards during the post-intensive care period: The PROSPECT-I study. Clin Nutr. 2022 Oct;41(10):2124-2134.
127. Moisey LL, Pikul J, Keller H, Yeung CYE, Rahman A, Heyland DK, et al. Adequacy of Protein and Energy Intake in Critically Ill Adults Following Liberation From Mechanical Ventilation Is Dependent on Route of Nutrition Delivery. Nutr Clin Pract. 2021 Feb;36(1):201-212.
128. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of oral intake in critically ill patients 1 week after extubation. J Am Diet Assoc. 2010 Mar;110(3):427-33.
129. Merriweather JL, Salisbury LG, Walsh TS, Smith P. Nutritional care after critical illness: a qualitative study of patients' experiences. J Hum Nutr Diet. 2016 Apr;29(2):127-36.
130. Naithani S, Whelan K, Thomas J, Gulliford MC, Morgan M. Hospital inpatients' experiences of access to food: a qualitative interview and observational study. Health Expect. 2008 Sep;11(3):294-303.
131. Chapple LS, Weinel LM, Abdelhamid YA, Summers MJ, Nguyen T, Kar P, et al. Observed appetite and nutrient intake three months after ICU discharge. Clin Nutr. 2019 Jun;38(3):1215-1220.
132. Chapple LA, Chapman M, Shalit N, Udy A, Deane A, Williams L. Barriers to Nutrition Intervention for Patients With a Traumatic Brain Injury: Views and Attitudes of Medical and Nursing Practitioners in the Acute Care Setting. JPEN J Parenter Enteral Nutr. 2018 Feb;42(2):318-326.
133. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualized nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019 Jun 8;393(10188):2312-21.

CHAPTER 2

2

Comparison of the Beacon and Quark indirect calorimetry devices to measure resting energy expenditure in ventilated ICU patients

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Abstract

Introduction

Critically ill patients in the Intensive care unit (ICU) should receive nutritional support matched to their metabolic needs as both under- and overfeeding energy has been shown to increase mortality. Critical illness can significantly affect metabolism. Consequently, resting energy expenditure (REE) can vary markedly during critical illness. Therefore, indirect calorimetry to estimate REE is recommended to determine energy requirements in individual ICU patients and to guide optimal nutritional support. Currently, the Quark metabolic monitor is considered the gold standard in our ICU, but novel mechanical support devices are also equipped with indirect calorimetry functionalities. This study aimed to evaluate the performance of a currently unevaluated device.

Methods

A cross-sectional analysis in mechanically ventilated patients was conducted in a mixed medical-surgical ICU. The primary outcome was a numerical and visual comparison of the performance of the Beacon indirect calorimeter to calculate REE compared to the Quark device using Bland Altman plots. Performance was evaluated using bias, precision, accuracy, and reliability. Secondary analysis included a comparison with REE estimated by predictive equations.

Results

Seventy-one measurements were obtained in 27 mechanically ventilated subjects. An underestimation by the Beacon device in calculated REE of -96.2 kcal/day (4.5%) was found. There was a bias towards higher VCO_2 and lower VO_2 values with Beacon as compared to Quark. The reliability of the Beacon was good, with an absolute intraclass correlation coefficient of 0.897 (95% CI 0.751-0.955; p=0.000). There was a poor correlation (<0.40) between the separate indirect calorimetry devices and most predictive equations. Only the Faisy predictive equations had good reliability (ICC 0.687, p=0.002).

Conclusions

Beacon indirect calorimetry accurately determined REE in mechanically ventilated critically ill patients compared to the gold standard in our ICU (Quark indirect calorimeter), although confidence intervals were wide. There was low bias and good reliability. On the other hand, predictive equations performed poorly compared to both devices, underestimating the true metabolic needs of mechanically ventilated ICU patients.

Introduction

Critically ill patients in the Intensive care unit (ICU) should receive nutritional support matched to their metabolic needs. In observational studies, both underfeeding and overfeeding energy increased morbidity and mortality among ICU patients (1-5). Critical illness can significantly affect metabolism, and energy expenditure (EE) can vary markedly during critical illness (6). Resting energy expenditure (REE) which accounts usually for 70% of total energy expenditure (TEE), can markedly increase after burns, sepsis, trauma, and surgery and in patients receiving vasopressors (4). However, REE also can decrease because of sedation, analgesics, or neuromuscular blocking agents (7). Predictive equations – such as the Harris-Benedict and Penn state University equations - are commonly used in clinical settings to predict REE (8-11). However, predictive equations are population-based averages, have low accuracy rates compared with indirect calorimetry, and are unreliable to predict EE in individual patients (4, 11-15). This lack of adequate methods to determine energy requirements poses a serious challenge to clinicians since these targets are used to guide nutritional support (16). Therefore, the recent European Society for Clinical Nutrition and Metabolism (ESPEN) adult ICU guideline recommends indirect calorimetry to estimate EE during critical illness to determine the energy requirements in individual ICU patients and to guide optimal nutritional support (17).

Indirect calorimetry

REE can be estimated with the Weir equation via oxygen consumption (VO_2) and carbon dioxide production (VCO_2), measured with indirect calorimetry.

For decades, the Deltatrac Metabolic Monitor (Datex, Helsinki, Finland; hereafter: Deltatrac) was considered the "gold standard" indirect calorimeter for critical care patients because VO_2 and VCO_2 measurements in ventilated patients were equivalent to mass spectrometry results (19,20). Unfortunately, Deltatrac is no longer manufactured, and several new devices have been introduced, relying on breath-by-breath analysis instead of the mixing chamber method used in the Deltatrac device. The QUARK RMR (COSMED, Rome, Italy; hereafter: Quark) has been validated – along with the CCM express (Medgraphics, Milano, Italy) – against the Deltatrac in mechanically ventilated patients (5,21-23). However, the Quark is a cumbersome device, requiring a time and personnel consuming user-assisted calibration procedure before each use.

Currently, a novel mechanical support device designed as a continuously Intensive Care Clinical Advisory system for ventilated patients, was equipped with indirect calorimetry functionalities as well. This Beacon Care system (Mermaid Care Company, Denmark; hereafter called: Beacon) works with any ICU ventilator and requires no installation but

only a virtual training of one hour to use the system (24). Until now, only one study has been published evaluating reliability and agreement between the Beacon and another indirect calorimetry device, i.e., Ecovx (GE Healthcare, Helsinki, Finland) (25). It was concluded that Beacon measurements were within-day reliable up to FiO_2 fractions of 0.85. That study was conducted in healthy subjects in sitting positions and not in critically ill and mechanically ventilated ICU patients, which warrants further evaluation of the device.

Therefore the primary aim of the present study was to test the performance of the Beacon device in measuring VO_2 consumption and VCO_2 production, and determining REE, compared with the current gold standard in our ICU (the Quark). Additionally, measurements were compared with REE estimations by predictive equations.

Materials and methods

Study design and study participants

A cross-sectional analysis was conducted in critically ill ICU patients in Gelderse Vallei hospital (ZGV) from September 17, 2018, till April 5, 2019. Adult patients (aged ≥18 years) being mechanically ventilated for ≥48 hours were eligible. After signing the informed consent by the patient or legal representative, patients were enrolled. Patients with high levels of mechanical ventilatory support (*i.e.,* fraction of inspired oxygen (FiO_2) >0.6 or positive end-expiratory pressure (PEEP) >12 cmH_2O) or ventilated in prone position were excluded from the study for patient safety and technical reasons, as well as patients with an acute respiratory distress syndrome (ARDS) as defined by the Berlin definition (26). Moreover, patients with unspecified amounts of air leakage (such as uncuffed tracheostomy cannula, endotracheal tube cuff leaks, tracheoesophageal fistulae, subcutaneous emphysema, or chest tube drainage) or a body temperature making an accurate measurement impossible (<36 or >42 degrees Celsius) were excluded. Each subject served as his/her control. The Medical Ethical Committee of ZGV approved the study (protocol number 1807-131).

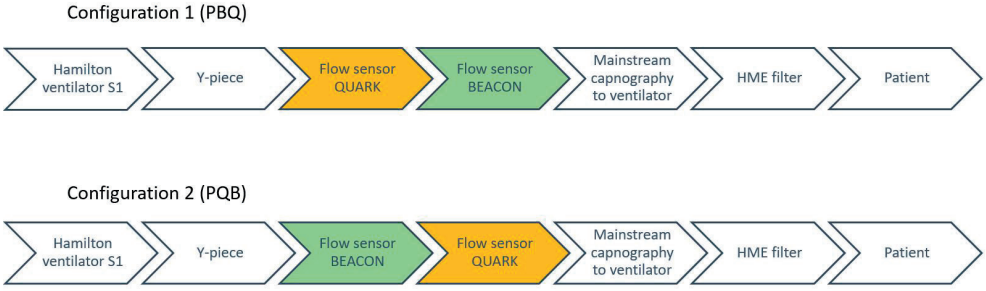
Study procedure

All measurements were performed by two investigators (SA and HSB), and study data were recorded. To ensure reliable, valid, and representative assessment of REE, subjects were not allowed to be engaged in any physical activity (such as physiotherapy) nor receive any form of renal replacement therapy as well as changes in ventilatory support (except for changes in FiO_2) two hours before the measurements. Furthermore, no inhalation drugs were administered during actual measurements. For safety reasons,

blood gasses were obtained before each measurement and indirect calorimetry was not performed when pH was below 7.3.

The measurements were performed with sampling lines from both Beacon and Quark calorimetry devices simultaneously in place. A pilot study on four subjects was performed to determine the optimal position for both devices. It was observed that REE calculations by the two devices were different based on the positions of the sampling lines (mean difference 224.3 kcal/day, SD 146.1 kcal/day). Therefore, two consecutive measurements in a computer-generated random order were performed, either Patient-Beacon-Quark (PBQ) configuration or Patient-Quark-Beacon (PQB) configuration (**Figure 1**). Conditions remained unchanged between the separate configuration measurements. After reaching a steady-state, each measurement was performed for at least 15 minutes per configuration. Recordings from the first 5 minutes and unstable conditions were excluded. A set of two configurations was defined as a single measurement day.

Figure 1. Measurement configurations



Two consecutive measurements in a computer-generated random order were performed, either Patient-Beacon-Quark (PBQ) configuration or Patient-Quark-Beacon (PQB) configuration (and vice versa). Conditions remained unchanged between the separate configuration measurements.

Measurements were performed on three subsequent days. Room temperature was maintained between 20-22°C during measurements. Both devices were calibrated (gas and flow/volume calibration procedures) before commencing measurements according to the user's manual provided by the manufacturer.

Study devices: the Quark and Beacon indirect calorimeters

Both Quark and Beacon functions are based on breath-by-breath gas analysis techniques (24,27). The disposable flow sensors – attached to the patient-ventilator circuit – trap small amounts of inhaled and exhaled gases via gas sampling lines. This technique is used to measure flow: VCO_2 (in mL/min) and VO_2 (in mL/min). The inbuilt software uses these measurements to calculate the respiratory exchange ratio (RER: VCO_2/VO_2)

and REE (kcal/day) in both devices. The RER is an estimate for the respiratory quotient (RQ)) when ventilatory parameters and acid-base balance are stable (20). RER ranges in physiologic circumstances between 0.67 and 1.2 and depends on the composition of (non)nutritional intake (20,28,29).

The formula used by the Quark device to calculate REE is similar to the Weir equation:

$$REE = [(3.9 \times VO_2 \text{ (in mL/min)}) + (1.1 \times VCO_2 \text{ (in mL/min)})] \times 1440.$$

The Beacon used another equation:

$$REE = 5.5 \times VO_2 \text{ (in mL/min)} + 1.76 \times VCO_2 \text{ (in mL/min)} - 1.99 \times \text{urinary nitrogen (UN)}.$$

As UN was set to 13 by the manufacturer, this can be further simplified to:

$$REE = 5.5 \times VO_2 \text{ (in mL/min)} + 1.76 \times VCO_2 \text{ (in mL/min)} - 25.87$$

Data collection

Data collection from the electronic patient documentation system included demographic and clinical baseline characteristics and prognostic scores, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores. Data extraction was performed using queries searching the ICU patient data management system (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (Neozis; MI Consultancy, Katwijk, The Netherlands). These parameters of interest are routinely collected during standard clinical care, and therefore imposed no burden to patients. During measurements, additional information regarding vital parameters, Glasgow Coma Scale (GCS) and ventilator mode and settings were recorded, including respiratory rate (breaths/min), body temperature (°C), PEEP (mmH_2O) and FiO_2 (%). Data verification was conducted manually.

Sample size

Using R software, a sample size of 20 patients was calculated (mean difference 224.3 kcal/day, standard deviation (SD) 146.1 kcal/day, alpha 0.05 and power of 0.8). As the study subjects are ICU patients, an estimated dropout rate of 10% was added to the calculated sample size. The final sample size was calculated as 22 patients.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA; 2016). Discrete variables were displayed as proportions. Continuous

variables were reported as means, including standard deviations (SD) or, in the case of non-normal distribution, as medians with interquartile ranges (IQR). P-values below 0.05 were considered statistically significant.

Primary data analysis

Primary data analysis included a numerical and visual comparison (using Bland Altman plots) of the Beacon's performance compared to the Quark device in measuring VO_2 consumption, VCO_2 production and REE calculation. Because the conditions between the separate configuration measurements were kept constant and unaltered, only measurements from the configurations with the device of interest closest to the patient were used for final analysis to minimize the concurrent effect of gas sampling (i.e., PQB for the Quark and PBQ for the Beacon, respectively).

Bias and precision were calculated to assess accuracy. Bias was defined as the mean difference between both devices; a bias of <10% was considered acceptable. Precision was visualized by the upper and lower limits of the 95% confidence interval (95% CI) in the Bland Altman plots (limits of agreement, LoA). In addition, agreement (reliability) between both devices was assessed by calculating the absolute intraclass correlation coefficient (ICC). Reliability was considered poor with an ICC <0.4, fair when $0.4 \leq ICC < 0.6$, good when $0.6 \leq ICC < 0.8$ and excellent when ICC was ≥ 0.8.

All calculations were corrected for repeated measures using mixed models.

Secondary data analysis

Secondary data analysis included the performance of eight frequently used predictive equations compared Beacon and Quark indirect calorimetry. The FAO/WHO/UNU, Harris-Benedict, 25 kcal/kg/day, Penn State 1998 & 2003, Mifflin-St Jeor, Ireton-Jones and Faisy equations were used to calculate REE manually and compared to the REE calculations by the Beacon device and Quark (see **Supplement 1**)(8,9,30-33).

Predictive equations were adjusted for under- and overweight patients with a Body mass index (BMI) of <18.5 or > 27 kg/m^2, respectively. In these cases, weight was adjusted to ideal body weight at a BMI of 18.5 or 27 kg/m^2.

Results

During the study period, ninety-seven mechanically ventilated patients were eligible for inclusion; of these, informed consent was obtained from 28 patients or their legal representatives. One patient refused participation after the family initially signed informed consent, leaving a total of 27 patients in this study.

The demographic and baseline patient characteristics are summarized in **Table 1**. Twenty patients (74.1%) were male. The median age was 71 (IQR 61-78) years, and BMI varied between 20.2 and 44.4 kg/m^2 (median 27.8 kg/m^2; IQR 24.9-31.0). The median APACHE II and SOFA scores on ICU admission were 21 and 7, respectively. Admission types were unequally distributed among the population: 17 (63%) were medical, 10 (37%) were surgical.

Table 1. Baseline characteristics

Gender (male)	*N (%)*	20 (74.1)
Age (years)	*Median [IQR]*	71 [61-78]
BMI on admission (kg/m^2)	*Median [IQR]*	27.8 [24.9-31.0]
Type of admission (medical)	*N (%)*	17 (63)
APACHE II score on admission	*Median [IQR]*	21 [17-24]
SOFA score on admission	*Median [IQR]*	7 [6-10]
NUTRIC score on admission	*Median [IQR]*	5 [4-6]
SAPS II score	*Median [IQR]*	45 [38-53]
Length of ICU stay (days)	*Median [IQR]*	15 [10-38]
Duration of mechanical ventilation (hours)	*Median [IQR]*	286.0 [148.6-588.8]
Intravenous sedation during measurements (yes)	*N (%)*	13 (48.1)
Ventilator mode during measurements	*N (%)*	
-P-CMV		6 (8.3%)
-ASV		6 (8.3%)
-PS		60 (83.3%)
Type of feeding	*N (%)*	
-Enteral		25 (92.6)
-Enteral/parenteral		2 (7.4)
-Parenteral		0 (0.0)

N = number of patients; IQR = interquartile range; BMI = body mass index; APACHE II = Acute Physiology And Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; NUTRIC = Nutrition Risk in Critically Ill; SAPS = Simplified Acute Physiology Score; ICU = Intensive Care Unit; P-CMV = Pressure Control, Controlled Mandatory Ventilation; ASV = Adaptive Support Ventilation; PS = Pressure Support.

Measurements

A total of 72 measurements was performed. One measurement was excluded for technical reasons (RER <0.6). Seventy-one measurements in 27 subjects were included for further analysis. Not all subjects could be measured on three consecutive days. In seven subjects, only one (n=3) or two (n=4) measurements were obtained: they were extubated before consecutive measurements or passed away. In 42 measurement sessions (59%), the configuration patient-Quark-Beacon was carried out first (p=0.377).

Periprocedural, patients received intravenous sedation, analgesia, or anxiety-reducing medication during 78.9% (56/71) of the measurements. During 23 of these measurements, patients were deeply sedated with propofol or midazolam (Richmond Agitation Sedation Scales (RASS) -4/-5).

Over the measurement days, patients received less sedation and vasopressors and had decreasing leukocyte counts, although these differences were minor and not statistically significant (see **Supplement 2**).

Primary outcome: performance of the Beacon device

Quark measurements were used as reference. A significant interaction (p=0.000) between the Beacon device and configuration type was found as illustrated in **Supplement 3**.

Mean measured VCO_2 were 229.9 (standard error (SE) 26.8) and 203.2 (SE 14.1) mL/min for Quark and Beacon, respectively, in configuration Patient-Quark-Beacon. For the configuration Patient-Beacon-Quark this was 214.7 (SE 14.1) and 246.9 (SE 8.8) mL/min, respectively (**Table 2; Supplement 4a**).

Table 2. Mean measured VCO_2 and VO_2 (mL/min) and calculated REE (kcal/day) [over the measurement days]

		estimated means	SE	95% CI	
PQB	**Quark**				
	VCO_2	229.9	26.8	176.5	283.3
	VO_2	312.3	30.8	251.1	373.4
	REE	2118.1	211.9	1696.5	2539.8
	Beacon				
	VCO_2	203.2	14.1	175.0	231.5
	VO_2	244.8	16.1	212.5	277.0
	REE	1681.0	111.2	1457.7	1904.3
PBQ	**Quark**				
	VCO_2	214.7	14.1	186.4	243.0
	VO_2	294.7	16.1	262.5	326.9
	REE	1987.4	111.2	1764.2	2210.7
	Beacon				
	VCO_2	246.9	8.2	229.0	264.8
	VO_2	290.7	10.0	270.5	310.9
	REE	2022.0	69.5	1880.8	2163.1

SE = standard error; 95% CI = 95% confidence interval; PQB referring to configuration Patient-Quark-Beacon; PBQ referring to configuration Patient-Beacon-Quark; VCO_2 = volume of carbon dioxide expired (in mL/min); VO_2 = volume of oxygen inspired (in mL/min); REE = resting energy expenditure (in kcal/day).

Concerning oxygen uptake measurements, mean measured VO_2 were 312.3 (SE 30.8) and 244.82 (SE 16.1) mL/min for Quark and Beacon, respectively, in configuration Patient-Quark-Beacon. For the configuration Patient-Beacon-Quark this was 294.7 (SE 16.1) and 290.7 (SE 10.0) mL/min, respectively (**Table 2; Supplement 4b**).

Table 3. Bias and precision of the Beacon device

	Mean difference*	SE	SD	95% CI**	
REE	-96.2	32.6	274.6	-634.4	442.0
VCO_2	17.0	4.1	34.1	-49.8	83.8
VO_2	-21.5	4.7	39.2	-98.3	55.3
RQ	0.12	0.009	0.08	-0.04	0.28

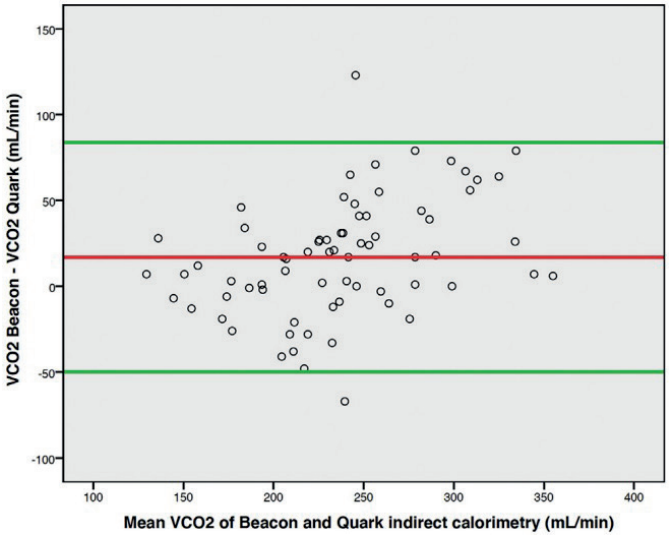
SE = standard error; SD = standard deviation; 95% CI = 95% confidence interval; REE = resting energy expenditure (in kcal/day); VCO_2 = volume of carbon dioxide expired (in mL/min); VO_2 = volume of oxygen inspired (in mL/min); RQ = respiratory quotient (VCO_2/VO_2);

**Also defined as bias; Beacon compared to Quark device;*

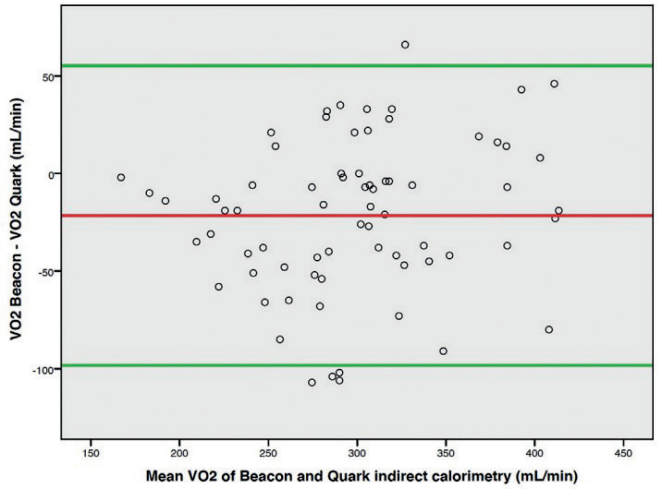
***Also defined as precision (=bias ± (1,96 × SD)).*

The mean difference in VCO_2 and VO_2 measurements by the Beacon device compared to Quark were +17.0 (SE 4.1) and -21.5 (SE 4.7) mL/min, respectively (**Table 3**). Bias and precision are visualized in the Bland-Altman plots (**Figure 2a-c**). For the Bland-Altman plots, only measurements from the configurations with the device of interest closest to the patient were used to minimize the concurrent effect of gas sampling (i.e., for the Quark PQB and for the Beacon PBQ, respectively).

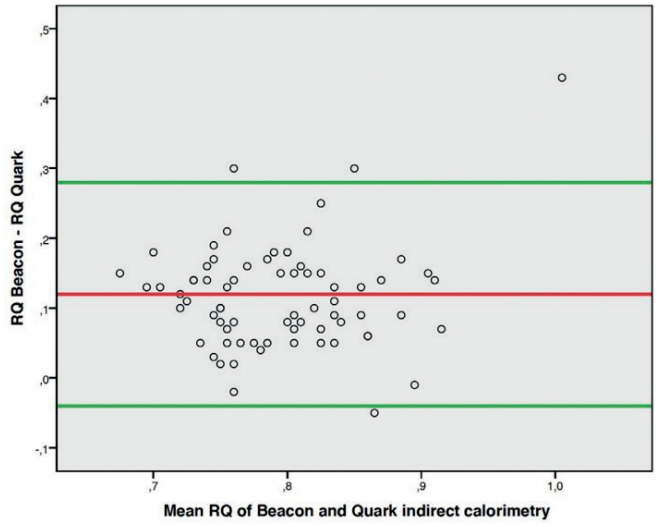
Figure 2a-c. Bland-Altman plots of VCO_2, VO_2 and RQ by both indirect calorimeters
A.



B.



C.



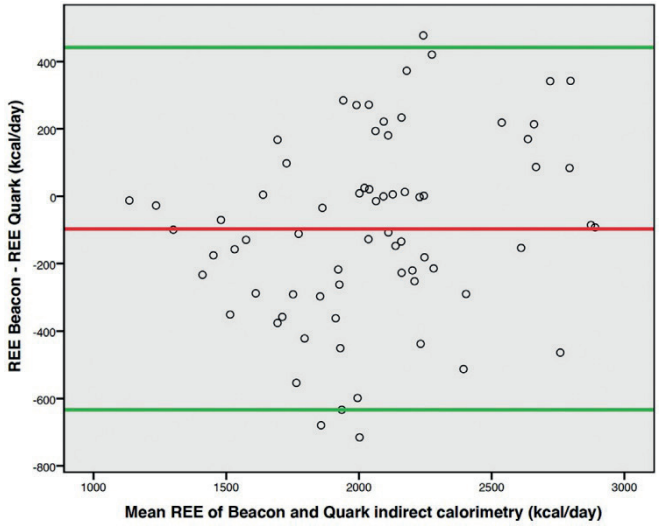
Red line = mean difference = bias;
Green lines = limits of agreement = bias ± (1.96 × SD) = precision.

REE calculations

Mean calculated REE was 2118.1 (SE 211.9) and 2022.0 (SE 69.5) kcal/day for Quark and Beacon, respectively, in their configurations closest to the patient (Patient-Quark-Beacon and Patient-Beacon-Quark respectively; see also **Table 2 & Supplement 4c**). Comparisons between REE calculations are illustrated in **Figure 2d**. The mean difference in REE calculation between Beacon and Quark was -96.2 (SE 32.6) kcal/day, resulting in a

bias of 4.5%. When applying the same formula (Weir) for both devices to calculate REE, the mean difference reduced to -73.9 (SE 31.3) kcal/day. This corresponds with a bias of 3.5%.

Figure 2d. Bland-Altman plot of REE measured by Quark and Beacon indirect calorimeters



Red line = mean difference = bias;
Green lines = limits of agreement = bias ± (1.96 × SD) = precision.

The Beacon device under- and overestimated REE in respectively 62.0% and 36.6% of cases. Reliability was good with an absolute intraclass correlation coefficient of 0.897 (95% CI 0.751-0.955; p=0.000).

Secondary outcomes: predictive equations

Predictive equations

Numerical comparisons between instruments and predictive equations are presented in **Table 4**. There was a poor correlation (<0.40) between the separate indirect calorimetry devices and most predictive equations. Reliability was fair for the weight adjusted Penn 1998 and Penn 2003 equations (ICC 0.574 and 0.495, respectively, compared to the Beacon device); only the Faisy and weight adjusted Faisy predictive equations performed good (ICC 0.636, p=0.007 and ICC 0.687, p=0.002, respectively, compared to the Quark device).

Table 4. Indirect calorimetry compared to predictive equations

		Mean difference with….		Absolute ICC			
	Mean REE	**...REE Q**	**...REE B**	**Quark**	***p-value***	**Beacon**	***p-value***
Quark	2118.1	NA	96.2	1.000	NA	0.897	0,000
Beacon	2021.9	-96.2	NA	0.897	0.000	1.000	NA
FAOWHO	1648.6	-469.4	-373.4	0.156	0.159	0.110	0.318
FAOWHO_IBW	1571.9	-546.1	-450.1	0.138	0.120	0.142	0.218
Harris Benedict	1602.8	-515.2	-419.2	0.158	0.152	0.147	0.249
Harris Benedict_IBW	1497.6	-620.4	-524.4	0.119	0.117	0.150	0.165
25 kcal/kg	2129.6	11.6	107.6	0.313	0.180	0.161	0.330
25kcal/kg_IBW	1924.8	-193.2	-97.2	0.434	0.041	0.391	0.103
Penn1998	2018.1	-99.9	-3.9	0.530	0.027	0.468	0.062
Penn1998_IBW	1902.4	-215.6	-119.6	0.564	0.004	0.574	0.013
Penn2003	1846.2	-271.8	-175.8	0.480	0.013	0.467	0.042
Penn2008_IBW	1756.8	-361.2	-265.2	0.451	0.002	0.495	0.011
Mifflin	1546.8	-571.2	-475.2	0.153	0.112	0.148	0.214
Mifflin_IBW	1464.9	-653.1	-557.1	0.135	0.072	0.163	0.127
Ireton	1622.7	-495.3	-399.3	0.081	0.285	0.086	0.345
Ireton_IBW	1581.7	-536.3	-440.3	0.075	0.270	0.103	0.294
Faisy	2132.9	14.9	110.9	0.636	0.007	0.514	0.032
Faisy_IBW	2067.4	-50.6	45.4	0.687	0.002	0.605	0.011

ICC = intraclass correlation coefficient (two-way mixed, absolute agreement); REE = resting energy expenditure; B = Beacon; Q = Quark; NA = not applicable; IBW = ideal body weight.

Discussion

The primary aim of this study was to evaluate the performance of the Beacon indirect calorimetry device in measuring VCO_2 and VO_2 and determination of REE in mechanically ventilated ICU patients. There was a bias towards higher VCO_2 and lower VO_2 values with Beacon compared to Quark (mean difference +17.0 ml/min and -21.5 ml/min respectively), although not statistically significant. Mean REE was underestimated by 96.2 kcal/day by the Beacon device compared to the reference Quark device; a bias of 4.5%. Of note, the indirect calorimeters use different formulas to calculate REE. When using the Weir formula for the Beacon device as well, this mean difference reduced to -73.8 (SE 31.3) kcal/day, lowering its bias to 3.5%. The Beacon device under- and overestimated the REE in respectively 62.0% and 36.6% of cases. Reliability was good with an absolute intraclass correlation coefficient of 0.897 (95% CI 0.751-0.955; p=0.000).

Mean differences in REE calculations by Beacon compared to Quark were more prominent for the separate configurations: -437.2 (SE 31.0; p=0.000) kcal/day and 34.5 (SE 30.4; p=0.260) kcal/day, for PQB and PBQ respectively. This observation may be

explained by the position of the flow sensors of both devices. In the PQB configuration, the Quark flow sensor is positioned closer to the patient than the Beacon flow sensor. In this way, the Beacon flow sensor is influenced by Quark's gas sampling, resulting in lower REE calculations (and vice versa for the PBQ configuration).

Because the conditions between the separate configuration measurements were kept constant and unaltered, only measurements from the configurations with the device of interest closest to the patient were used for the Bland-Altman plots to minimize the concurrent effect of gas sampling (i.e. for the Quark PQB and for the Beacon PBQ, respectively).

Calculated REE increased over the measurement days, especially between days 1 and 2 (+174.6 kcal/day for both devices). This may be due to less sedation and mechanical support and increased in condition (inflammatory parameters), although these changes were not statistically significant (**Supplement 2**).

To date, this is the first study of indirect calorimetry in ICU patients using the Beacon device. Poulsen *et al.* compared the Beacon device with another breath-by-breath indirect calorimeter (Ecovx) in healthy subjects (2019). They demonstrated that the Beacon device measured VO_2, and VCO_2 (and calculated REE) at 21%–85% FiO_2 reliably, but with increasing bias at FiO_2 levels of ≥85% (25). We could extend this to the population of critically ill mechanically ventilated patients.

Furthermore, this is the first study comparing predictive equations with the Beacon indirect calorimeter. Predictive equations perform poorly, mainly because they contain static estimations of REE and do not reflect the (dynamic) energy demands of ICU patients.

It was observed that confidence intervals were wide, indicating that – although the mean difference between the two devices may be only 96.2 kcal/day – the Beacon can make a large measurement error. The large standard deviations (and wide 95% CI's) in our study are either due to the sensitivity of measurements in ICU patients, the relatively small and heterogeneous study sample, or a combination of both. Even minor disturbances resulted in patients' unrest or anxiety, ultimately increasing his/her energy expenditure. The standard errors were the largest for the Beacon device measurements over the separate days when in the closest position to the patient (configuration PBQ). This result might be due to different reliability or more variable/fewer stable measurements. A follow-up study will allow us to (re)evaluate measurement reliability, and the effect of the configuration and REE formula use.

Strengths

The main strength of the current study includes that it was performed in ICU patients, directly reflecting the (dynamic) metabolic needs of a patient group, which is insufficiently considered when using (static) predictive equations. Although the study population was relatively small, we could include repeated measurements for most study participants. Several aspects of the Beacons performance were highlighted, including bias, precision, accuracy, and reliability.

Limitations

The most important limitation of this study is the lack of validation with the absolute gold standard at the time of the study: the Deltatrac. However, the Quark has been validated against this device and was considered the gold standard in this study. The second limitation was measurements on three separate days, resulting in changes of the (clinical) condition leading to statistical bias. A final limitation of this study is its generalizability, as the two indirect calorimeters were compared in ICU subjects.

Repeating this study in healthy persons will allow evaluating accuracy, bias, and reliability without measuring confounders by disease and sedation. Moreover, as already suggested by Poulsen *et al.*, further studies need to evaluate accuracy, bias and precision at high levels of FiO_2 (≥85%) (25). Finally, validation against next generation indirect calorimeters (Q-NRG) which are currently considered gold standard, is necessary (34).

Conclusion

Beacon indirect calorimetry is accurate compared to the current gold standard in our ICU (Quark indirect calorimeter), with a mean underestimation in calculated REE of only -96.2 kcal/day (4.5%). However, confidence intervals were wide, indicating the risk of large measurement errors. Moreover, there was bias towards higher VCO_2 and lower VO_2 values with Beacon compared with Quark, although not statistically significant. Reliability was good, with an absolute intraclass correlation coefficient of 0.897. In contrast, there was a poor correlation (<0.40) between the separate indirect calorimetry devices and most predictive equations. Therefore, predictive equations should not be used to estimate metabolic needs of mechanically ventilated ICU patients.

References

1. McClave SA, Lowen CC, Kleber MJ, Nicholson JF, Jimmerson SC, McConnell JW, et al. Are patients fed appropriately according to their caloric requirements? JPEN J Parenter Enteral Nutr. 1998 Nov-Dec;22(6):375-81.
2. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014 Dec 14;18(6):701.
3. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016 Nov 10;20(1):367.
4. Segadilha NLAL, Rocha EEM, Tanaka LMS, Gomes KLP, Espinoza REA, Peres WAF. Energy Expenditure in Critically Ill Elderly Patients: Indirect Calorimetry vs Predictive Equations. JPEN J Parenter Enteral Nutr. 2017 Jul;41(5):776-784.
5. Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. J Intensive Care. 2021 Jan 12;9(1):8.
6. Weijs PJ, Wischmeyer PE. Optimizing energy and protein balance in the ICU. Curr Opin Clin Nutr Metab Care. 2013 Mar;16(2):194-201.
7. Schlein KM, Coulter SP. Best practices for determining resting energy expenditure in critically ill adults. Nutr Clin Pract. 2014 Feb;29(1):44-55.
8. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. Proc Natl Acad Sci U S A. 1918 Dec;4(12):370-373.
9. Frankenfield D, Smith JS, Cooney RN. Validation of 2 approaches to predicting resting metabolic rate in critically ill patients. JPEN J Parenter Enteral Nutr. 2004 Jul-Aug;28(4):259-64.
10. Melzer K, Laurie Karsegard V, Genton L, Kossovsky MP, Kayser B, Pichard C. Comparison of equations for estimating resting metabolic rate in healthy subjects over 70 years of age. Clin Nutr. 2007 Aug;26(4):498-505.
11. Flack KD, Siders WA, Johnson L, Roemmich JN. Cross-Validation of Resting Metabolic Rate Prediction Equations. J Acad Nutr Diet. 2016 Sep;116(9):1413-1422.
12. De Waele E, Opsomer T, Honoré PM, Diltoer M, Mattens S, Huyghens L, et al. Measured versus calculated resting energy expenditure in critically ill adult patients. Do mathematics match the gold standard? Minerva Anestesiol. 2015 Mar;81(3):272-82.
13. Wichansawakun S, Meddings L, Alberda C, Robbins S, Gramlich L. Energy requirements and the use of predictive equations versus indirect calorimetry in critically ill patients. Appl Physiol Nutr Metab. 2015 Feb;40(2):207-10.
14. Tignanelli CJ, Andrews AG, Sieloff KM, Pleva MR, Reichert HA, Wooley JA, et al. Are Predictive Energy Expenditure Equations in Ventilated Surgery Patients Accurate? J Intensive Care Med. 2019 May;34(5):426-431.
15. Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: A retrospective validation. Clin Nutr. 2019 Jun;38(3):1206-1210.
16. Lambell KJ, Tatucu-Babet OA, Chapple LA, Gantner D, Ridley EJ. Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care. 2020 Feb 4;24(1):35.
17. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019 Feb;38(1):48-79.

18. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949 Aug;109(1-2):1-9.
19. Tissot S, Delafosse B, Bertrand O, Bouffard Y, Viale JP, Annat G. Clinical validation of the Deltatrac monitoring system in mechanically ventilated patients. Intensive Care Med. 1995 Feb;21(2):149-53.
20. Stapel SN, de Grooth HJ, Alimohamad H, Elbers PW, Girbes AR, Weijs PJ, et al. Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: proof of concept. Crit Care. 2015 Oct 22;19:370.
21. Graf S, Karsegard VL, Viatte V, Heidegger CP, Fleury Y, Pichard C, et al. Evaluation of three indirect calorimetry devices in mechanically ventilated patients: which device compares best with the Deltatrac II(®)? A prospective observational study. Clin Nutr. 2015 Feb;34(1):60-5.
22. Sundström Rehal M, Tjäder I, Rooyackers O, Wernerman J. Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr. 2013 Feb;32(1):118-21.
23. Sundström Rehal M, Fiskaare E, Tjäder I, Norberg Å, Rooyackers O, Wernerman J. Measuring energy expenditure in the intensive care unit: a comparison of indirect calorimetry by E-sCOVX and Quark RMR with Deltatrac II in mechanically ventilated critically ill patients. Crit Care. 2016 March 5;20:54.
24. Mermaid Care. Beacon Caresystem: Advisory system for ICU Ventilation and Nutrition [internet]. Available from: http://beaconcaresystem.com/beacon-caresystem/_[Accessed September 16, 2021].
25. Poulsen MK, Thomsen LP, Kjaergaard S, Rees SE, Karbing DS. Reliability of, and Agreement Between, two Breath-by-Breath Indirect Calorimeters at Varying Levels of Inspiratory Oxygen. Nutr Clin Pract. 2019 Oct;34(5):767-774.
26. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33.
27. Cosmed, the Metabolic Company. Quark RMR. The gold standard for metabolic measurement in applied human physiology research [internet]. Available from: https://www.cosmed.com/en/products/indirect-calorimetry/quark-rmr [Accessed September 16, 2021].
28. Branson RD. The measurement of energy expenditure: Instrumentation, practical considerations, and clinical application. Respir Care. 1990 35:640-659.
29. Haugen HA, Chan LN, Li F. Indirect calorimetry: a practical guide for clinicians. Nutr Clin Pract. 2007 Aug;22(4):377-88.
30. FAO/WHO/UNU Expert Consultation. Equations for the prediction of basal metabolic rate [internet]. Available from: http://www.fao.org/3/aa040e/AA040E15.htm [Accessed September 16, 2021].
31. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990 Feb;51(2):241-7.
32. Faisy C, Guerot E, Diehl JL, Labrousse J, Fagon JY. Assessment of resting energy expenditure in mechanically ventilated patients. Am J Clin Nutr. 2003 Aug;78(2):241-9.
33. Walker RN, Heuberger RA. Predictive Equations for Energy Needs for the Critically Ill. Resp Care 2009 April; 54(4):509-521.
34. Oshima T, Delsoglio M, Dupertuis YM, Singer P, De Waele E, Veraar C, et al. The clinical evaluation of the new indirect calorimeter developed by the ICALIC project. Clin Nutr. 2020 Oct;39(10):3105-3111.

Supplemental material

Supplement 1. Predictive equations

Equation	Age (y)	Male	Female
FAO/WHO/UNU	18-30	15.4×w - 0.27×h + 717	13.3×w + 3.34×h + 35
	30-60	11.3×w - 0.16×h + 901	8.7×w - 0.25×h + 865
	≥60	8.8×w + 11.28×h - 1071	9.2×w + 63.7×h - 302
Harris Benedict		66.4730 + 13.7516×w + 5.0033×h - 6.7550×a	655.0955 + 9.5634×w + 1.8496×h - 4.6756×a
25 kcal/kg/day		25×w	idem
Penn State 1998		1.1×HB +32×VE + 140×T_{max} - 5340	idem
Penn State 2003		0.85×HB + 33×VE + 175×T_{max} - 6433	idem
Mifflins-St Jeor		9.99×w + 6.25×h - 4.92×a + 5	9.99×w + 6.25×h - 4.92×a - 161
Ireton-Jones (revised)		1784 - 11×a + 5×w + 239×t + 804×b + 244	1784 - 11×a + 5×w + 239×t + 804×b
Faisy		8×w + 14×h + 32×VE + 94×T_{max} - 4834	idem

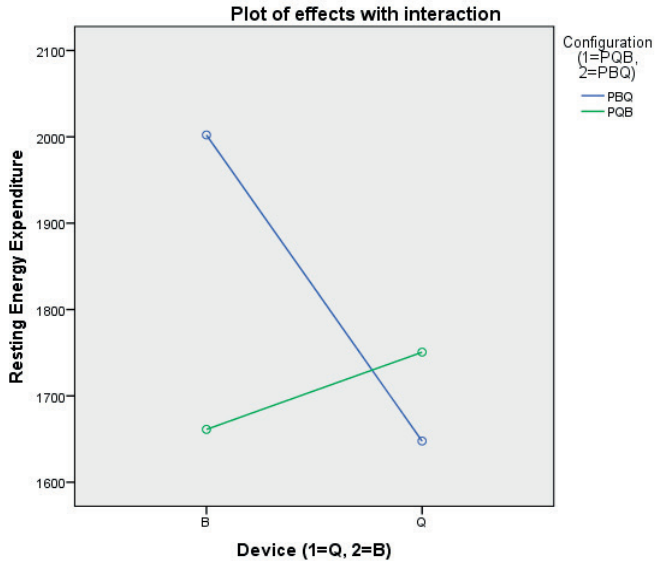
a = age (in years); h = height (in centimeters); w = weight (in kilograms); y = years;
HB = REE as calculated by Harris Benedict equation (kcal/day); T_{max} = (maximal) body temperature (degrees Celsius);
VE = minute ventilation (L/min); b = burn (0=absent; 1=present); t = trauma (0=absent; 1=present);
Of note: T_{max} and VE were averaged over the study days.

Supplement 2. Details of subsequent measurement days

		Day 1 (n=27)	Day 2 (n=24)	Day 3 (n=20)	*p-value***
Ventilator mode	*N (%)*				*0.834*
PS		22 (81.5)	19 (79.2)	18 (90.0)	
ASV		2 (7.4)	3 (12.5)	1 (5.0)	
P-CMV		3 (11.1)	2 (8.3)	1 (5.0)	
Body temperature (^{o}C)	*mean (SD)*	37.3 (0.9)	37.5 (0.9)	37.6 (0.9)	*0.549*
Heart rate (/min)	*mean (SD)*	88.3 (15.2)	92.5 (19.4)	87.9 (19.5)	*0.630*
Level (cmH_2O)	*median [IQR]*	9 [6-12]	8 [6-11.5]	9.5 [6-12]	*0.746*
PEEP (cmH_2O)	*median [IQR]*	8 [7-10]	9 [6-10]	8 [6-10]	*0.948*
FiO_2 (%)	*median [IQR]*	30 [30-35]	35 [30-38.8]	35 [26-40]	*0.454*
Minute volume (L/min)	*mean (SD)*	10.9 (3.3)	11.3 (2.4)	11.0 (2.9)	*0.858*
Respiratory rate (/min)	*mean (SD)*	20.7 (6.0)	23.1 (6.8)	22.2 (6.6)	*0.400*
Tidal volume (mL)	*mean (SD)*	534.6 (123.3)	506.4 (122.1)	478.3 (95.6)	*0.261*
Entidal CO_2 (kPa)	*mean (SD)*	5.1 (0.8)	5.0 (0.8)	5.2 (1.1)	*0.752*
Vasopressor use*	*median [IQR]*	0.01 [0.00-0.12]	0.00 [0.00-0.05]	0.00 [0.00-0.07]	*0.330*
Relaxantia (yes)	*N (%)*	1 (3.7)	0 (0)	0 (0)	*0.438*
RASS	*median [IQR]*	-3 [-4 to -1]	-3 [-4 to -1]	-1 [-3 to 0]	*0.233*
CRP (mg/L)	*median [IQR]*	128 [69-236]	123 [63-211]	138 [48-184]	*0.814*
Leukocyte count (x 10^9/L)	*median [IQR]*	13 [9.6-17.4]	11.8 [9.2-14.8]	11.8 [9.2-17.5]	*0.682*

PS = Pressure Support; ASV = Adaptive Support Ventilation; P-CMV = Pressure Control, Controlled Mandatory Ventilation; PEEP = Positive End-Expiratory Pressure; FiO_2 = Fraction of Inspired Oxygen; RASS = Richmond Agitation Sedation Scale; CRP = C-reactive protein;
N = number; SD = Standard deviation; IQR = interquartile range;
**in gamma norepinephrine;*
*** calculated using one-way ANOVA for parametric data; Kruskal-Wallis test for non-parametric data.*

Supplement 3. Illustration of interaction between Beacon device and configuration



As described in the manuscript, there is a significant interaction between the Beacon device and type of configuration.

Supplement 4. Mean measured VCO_2 and VO_2 (and calculated REE) over the measurement days

4a. Mean measured VCO_2 over the measurement days (mL/min)

	estimated means	SE	95% CI	
PQB				
Q1	219.0	36.7	146.0	291.9
Q2	241.7	37.1	168.0	315.4
Q3	223.5	22.9	178.1	268.9
PBQ				
Q1	203.8	28.1	147.9	259.7
Q2	226.5	28.4	169.9	283.1
Q3	208.3	14.3	180.0	236.7

	estimated means	SE	95% CI	
PQB				
B1	192.3	28.1	136.5	248.2
B2	215.0	28.4	158.4	271.7
B3	196.9	14.3	168.5	225.2
PBQ				
B1	236.0	24.5	187.2	284.8
B2	258.7	24.8	209.2	308.3
B3	240.5	10.7	219.3	261.8

4b. Mean measured VO_2 over the measurement days (mL/min)

	estimated means	SE	95% CI	
PQB				
Q1	301.8	50.0	203.4	400.1
Q2	323.6	50.2	224.8	422.4
Q3	302.3	41.5	220.5	384.0
PBQ				
Q1	284.2	26.8	231.5	336.9
Q2	306.0	27.0	252.9	359.2
Q3	284.7	18.3	248.6	320.7

	estimated means	SE	95% CI	
PQB				
B1	234.3	26.8	181.6	287.0
B2	256.1	27.0	203.0	309.2
B3	234.8	18.3	198.7	270.8
PBQ				
B1	280.2	17.2	246.5	314.0
B2	302.1	17.4	267.9	336.3
B3	280.7	8.7	263.6	297.8

4c. Mean calculated REE over the measurement days (kcal/day)

	estimated means	SE	95% CI	
PQB				
Q1	1698.7	103.1	1492.4	1905.2
Q2	1873.3	103.2	1666.7	2079.9
Q3	1752.0	69.0	1612.8	1891.3
PBQ				
Q1	1595.8	140.2	1316.4	1875.4
Q2	1770.4	140.3	1490.7	2050.1
Q3	1649.1	106.1	1436.8	1861.5

	estimated means	SE	95% CI	
PQB				
B1	1609.3	140.2	1329.9	1888.9
B2	1783.9	140.3	1504.2	2063.6
B3	1662.6	106.1	1450.3	1875.0
PBQ				
B1	1950.3	229.8	1494.4	2406.4
B2	2124.9	229.9	1668.7	2581.1
B3	2003.6	195.7	1614.8	2392.5

VCO_2 = volume of carbon dioxide expired (in mL/min); VO_2 = volume of oxygen inspired (in mL/min); REE = Resting energy expenditure (in kcal/day);
SE = standard error; 95% CI = 95% confidence interval; PQB referring to configuration Patient-Quark-Beacon; PBQ referring to configuration Patient-Beacon-Quark;
Q1, Q2, … referring to Quark measurements on measurement day 1, day 2, …
B1, B2, … referring to Beacon measurements on measurement day 1, day 2, …

CHAPTER 3

3

Video-assisted Placement of Enteral Feeding Tubes using the Integrated Real-Time Imaging System (IRIS)-technology in Critically Ill Patients

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Abstract

Introduction

In critically ill patients, nasogastric (NG) and nasojejunal (NJ) feeding tube placements are standard procedures. However, about 1.9% of blind narrow-bore tube insertions are malpositioned in the tracheopulmonary system, whereas endoscopically-guided placements are resource-intensive with long waiting times, adding up to delays until initiation of feeding. Video-assisted placement of NG and NJ enteral feeding tubes is suggested a superior alternative since enteral feeding tubes are placed at the bedside under direct visualization of anatomical landmarks using Integrated Real-Time Imaging System (IRIS-) technology.

Methods

A prospective cohort study in patients requiring enteral feeding was conducted in a mixed medical-surgical intensive care unit (ICU). The primary outcome was the optimal post-pyloric placement of IRIS feeding tubes, as confirmed by X-Ray studies. Secondary study parameters included gastric placement, feasibility, ease of use, and safety.

Results

Thirty-one feeding tubes were placed using IRIS-technology; one patient was excluded for analysis due to protocol violation. One procedure was terminated due to significant bleeding (epistaxis) and desaturation. Eighteen (58%) feeding tubes were optimally placed in post-pyloric position (including two past the ligament of Treitz), and 96.8% were properly placed when gastric placement should have been the goal. During insertion, tracheal visualization occurred in 27% of cases, and the IRIS feeding tube was repositioned early in the procedure without causing patient harm.

Conclusions

Real-time video-assisted post-pyloric feeding tube placement in critically ill ICU patients was successful in 58% of cases. A high success rate (96.8%) for gastric placement was achieved. It is suggested as an alternative for blind insertion, as immediate detection of tracheal placement and low rates of adverse events were encountered. However, the technique could be adapted to make it suitable for post-pyloric placement. This method potentially reduces the time and costs for personnel and X-rays obligatory for alternative techniques.

Introduction

Most critically ill patients admitted to the Intensive care unit (ICU) require enteral nutrition (EN), enteral administration of medication, or gastric decompression (1,2). It has been demonstrated that early enteral feeding (*i.e.,* within 24-48 hours after ICU admission) is beneficial in critically ill patients concerning infectious complications (relative risk 0.76, 95% confidence interval 0.59-0.97, $p < 0.03$), patient safety and outcomes (1,3,4). Gastric access is recommended by the European, American, and Canadian clinical nutrition guidelines as the standard approach (1,4-8). In patients with a high risk of aspiration (such as the absence of an intact gag reflex), proximal enteric fistulae, or in cases of persistent gastric feeding intolerance despite the administration of prokinetics, post-pyloric feeding should be considered, with post ligament of Treitz as the optimal position (1,9-11).

In ICUs, nasogastric (NG) and nasojejunal (NJ) feeding tube placements are standard procedures. Most NG feeding tubes are inserted blindly, whereas NJ feeding tubes are placed using a guided placement method, such as real-time electromagnetic signals (Cortrak) or endoscopically by gastroenterologists. However, these guided procedures frequently result in a significant delay in nutritional delivery due to the limited availability of qualified operators and equipment (10,12). Other disadvantages of endoscopic placement include the staffing costs (endoscopy team), distress and discomfort for the patient, sedation requirements, time-consuming appointments with different departments and – in some hospitals – the risk of transporting critically ill patients through the hospital (3,13).

Since most tube placements – except for endoscopic insertions – are usually conducted blindly, the final position should be confirmed before initiating nutritional therapy to avoid pulmonary misplacement, especially in mechanically ventilated patients who are at increased risk for tube misplacement due to unconsciousness and weakened cough reflex (14,19). Chest or upper abdominal X-ray is considered the gold standard (18,19). However, this technique results in radiation exposure and additional costs for each NG/NJ insertion (20,21). Moreover, it is not foolproof: between September 2005 and March 2010, a total number of 21 deaths and 79 other cases of harm due to misplaced NG tubes were reported to the National Patient Safety Agency, of which 45% were due to X-Ray misinterpretation (22,23). Other studies have reported death rates of 0.27% (24). Although a correct position may be confirmed on X-ray, migration of the feeding tube in the days after initial placement is a not rare complication (17,26).

Video-assisted placement of NG and NJ enteral feeding tubes is suggested as a better alternative to blind placement since enteral feeding tubes (either NG or NJ) are

placed under direct visualization of anatomical landmarks using Integrated Real-Time Imaging System (IRIS-) technology (hereafter called "IRIS feeding tubes"; Cardinal Health, Mansfield, MA, USA). These IRIS feeding tubes are equipped with a mini video camera at the distal tip, allowing real-time visualization of anatomic landmarks on an external portable monitor during tube insertion and thereby potentially eliminating the need for X-ray confirmation. Moreover, video-assisted insertion is proposed as an alternative to endoscopic placement, requiring less preparation time and less personnel, thus reducing costs. Besides, IRIS feeding tubes allow daily position checks by re-visualizing the gastric/jejunal mucosa, thereby minimizing the risk of aspiration resulting from an unrecognized tube migration (2). To date, only two studies on the use of camera-equipped feeding tubes have been published (27,28). In both studies, the intent was to place the tubes in the gastric position. Both studies conclude that IRIS technology provides direct visualization of anatomical landmarks avoiding pulmonary misplacement in 20-35% of cases (27,28).

This study aimed to investigate IRIS feeding tube performance for post-pyloric placement, as confirmed by X-ray studies. Secondary objectives included gastric placement, testing the overall feasibility of enteral feeding tube insertion using IRIS-technology and to evaluate safety. We hypothesized that NG/NJ tube placement under direct visualization using IRIS-technology is simple, safe and efficient in ICU-patients, providing identification of the esophagus and stomach (and small intestines if desired) guiding accurate placement.

Materials and methods

This prospective cohort study was conducted from May 5, 2019, until December 12, 2019, in critically ill patients admitted to a mixed medical-surgical ICU at Gelderse Vallei hospital (Ziekenhuis Gelderse Vallei (ZGV), in Ede, The Netherlands).

Study design and participants

Patients aged ≥18 years with an indication for enteral feeding and/or medication for at least 48 hours were eligible for inclusion. After obtaining informed consent from the patient or legal representative, patients were enrolled in consecutive order. Patients with previous upper gastrointestinal tract ((oro)pharynx, esophagus, gastric or small bowel) surgery were not eligible, as well as patients with a suspicion of upper gastrointestinal bleeding or stenosis. Moreover, patients with altered anatomy, basal skull fracture or a life expectancy of fewer than 48 hours were excluded. The number of patients to recruit was estimated at 30 subjects (15 per operator) to sufficiently analyze the primary study endpoints.

Insertion of the feeding tube

IRIS feeding tubes were inserted by strictly following a prescribed protocol. All tubes were attempted to be placed in the post-pyloric position. Tubes were placed by two trained physicians (AvZ and HSB). Both performed a training phase with a total of five cases each. Feeding tubes were available in two lengths: 109cm (10 French diameter) and 140cm (10 and 12 French diameters). An insufflation device was used whenever necessary to aid in feeding tube placement. Prokinetics were not routinely administered. In case of tracheal malpositioning or any other difficulties encountered, which could not be solved without retraction of the feeding tube, a new attempt was started after withdrawal of the feeding tube to the nostrils.

Following the insertion procedure, all tubes were secured with tape to the patient's nose. The tube position was checked by chest or upper abdominal X-ray (for study reasons). X-Rays were independently and blindly assessed by the operator and a radiologist (CvM). Enteral feeding and/or medication administration was only commenced after radiological confirmation of correct position. After X-Ray evaluation by the operator, the tube was retracted to the gastric position (confirmed by visualization of gastric mucosa) in patients without an indication for a post-pyloric feeding tube.

Follow-up

Complications and adverse events were recorded from the start until the end of the study period. Study participation ended immediately after removal of the IRIS feeding tube, either on purpose or accidentally.

To evaluate the feeding tube position and the IRIS-camera's ability to visualize the gastric/duodenal mucosa over time, daily screenshots were collected. This was performed until feeding tube removal or patient discharge from the ICU. When the IRIS feeding tube was still present on ICU discharge, patients were followed up in the general wards for complications and adverse events.

Questionnaires

After inserting the IRIS feeding tube, the operator completed a short questionnaire based on a standardized, summated and single usability metric (SUM, see **Supplement 1**)(29). Conscious patients were also asked to complete a short survey to assess how they experienced the procedure. Since there were no validated scales available to measure patients' satisfaction after enteral feeding tube placement, we composed a new questionnaire based on existing questionnaires measuring patient experience and satisfaction (**Supplement 1**)(30-33).

Outcome measures

The primary outcome of this study was the number (percentage) of optimally placed post-pyloric feeding tubes using the IRIS-technology, assessed by X-Ray studies. Secondary parameters included successful gastric placement, feasibility and ease of use (number of attempts needed and operator & patient evaluation), and safety parameters (number of patients with visualization of the trachea and the ability to identify the correct position during daily enteral feeding).

The primary outcome analysis was based on an intention-to-treat (ITT) analysis. The ITT population consisted of all patients who met eligibility criteria and were enrolled in the study and not considered training cases. Additional per-protocol (PP) analyses were carried out. The PP population consisted of all patients in the ITT population who had an IRIS feeding tube placed in gastric or jejunal space and correct position confirmed by X-Ray.

Data collection

Data collection included patient characteristics (age, gender, anthropometry, comorbidities), admission type (medical or surgical) and presence of mechanical ventilation, including information about the state of consciousness. Moreover, several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Nutrition Risk in the Critically Ill (NUTRIC)) on ICU admission were determined. On the procedural day, gastric residual volume (24h) and use of prokinetic agents were recorded. Data extraction was performed using queries searching the ICU patient data management system (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (Neozis; MI Consultancy, Katwijk, The Netherlands). These parameters of interest had been routinely collected during standard clinical care, and therefore imposed no burden or risk to patients. Data verification was conducted manually.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA; 2016). Discrete variables were displayed as proportions. Continuous variables were reported in means including standard deviations (SD) or, in case of non-normal distribution, in medians with interquartile ranges (IQR). Normality was assessed graphically (visual inspection of histograms and Q-Q plots) and numerically, using the Shapiro Wilk test. Z-values were calculated to determine kurtosis and skewness. A p-value below 0.05 was considered statistically significant.

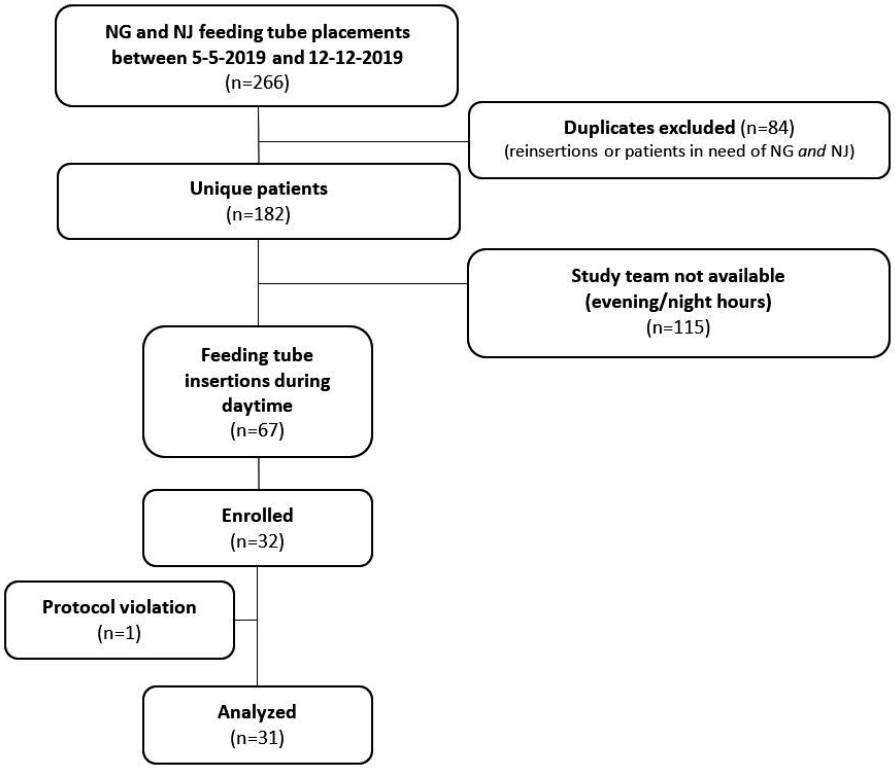
Ethical approval

The Institutional Review Board of ZGV approved the study (protocol number 1807-136).

Results

Between May 5, 2019, until December 12, 2019, a total of 182 unique patients needed an NG and/or NJ feeding tube for at least 48 hours. Of these, 115 patients had an urgent indication for tube insertion during evening or night shifts (17:00-8:00), which could not wait until the next working day. Therefore, 67 patients needed feeding tube insertion during daytime hours, when the study team was available. Of these, thirty-two patients were enrolled in the study (**Figure 1**). However, one patient was excluded due to a protocol violation (previous history of gastric bypass surgery that was not identified on ICU admission). The majority of patients were male (61%), overweight (median body mass index (BMI) 28.4 kg/m^2), non-surgical (71%), and had sepsis on ICU admission (51.6%). In five patients (16%), a post-pyloric feeding tube was clinically indicated; all others needed a gastric feeding tube (**Table 1**). Four patients (12.9%) had gastric residual volumes of >500mL/24 hours, and five patients (16.1%) were administered prokinetics on the day of feeding tube insertion.

Figure 1. Study flow chart



NG = nasogastric; NJ = nasojejunal; n = number.

Preprocedurally, about half of the study population (52%) already received intravenous sedation, analgesia and/or anxiety-reducing medication. Of these, nine patients (56%) were deeply sedated with propofol or midazolam (Richmond Agitation Sedation Scales (RASS) -4/-5). Others were prescribed dexmedetomidine or clonidine (n=3), or intravenous opioids (n=4). Due to unrest, a bolus of 5 mg midazolam was administered to three patients (10%) periprocedural. About 45% (n=14) were invasively mechanically ventilated, and nine patients (29%) received non-invasive mechanical ventilation. The other study participants were respiratory stable without any supplemental oxygen therapy (n=3) or were administered oxygen through an uncuffed tracheostomy (n=1) or nasal cannulae (n=4) (**Table 1**).

Table 1. Patient characteristics

Age (years)	*Median (IQR)*	71 (62-77)
Gender (male)	*N (%)*	19 (61)
Type of admission (medical)	*N (%)*	22 (71)
BMI on admission (kg/m^2)	*Median (IQR)*	28.4 (24.1-31.1)
APACHE II score on admission	*Median (IQR)*	20 (16-25)
SOFA score on admission	*Median (IQR)*	6 (5-8)
NUTRIC score on admission	*Median (IQR)*	5 (4-6)
Indication for post-pyloric feeding tube	*N (%)*	5 (16)
During procedure		
Intravenous sedation	*N (%)*	16 (52)
Propofol/midazolam (sedation level RASS -4/-5)		9 (56)
Dexmedetomidine/clonidine		3 (19)
Opioids		4 (25)
Oxygen therapy		
None	*N (%)*	3 (10)
Nasal cannula	*N (%)*	4 (13)
Non-invasive ventilation & High Flow Nasal Oxygen	*N (%)*	9 (29)
Uncuffed tracheostomy cannula	*N (%)*	1 (3)
Invasive mechanical ventilation	*N (%)*	14 (45)

IQR = interquartile range; N = number of patients; BMI = body mass index; APACHE II = Acute Physiology And Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; NUTRIC = Nutrition Risk in Critically ill; RASS = Richmond Agitation-Sedation Scale.

Primary outcome: success rates

A total of 30 IRIS feeding tubes were placed in the gastrointestinal tract (**Table 2**). One procedure was terminated due to significant bleeding (epistaxis) and desaturation (SaO_2 85%). In total, 18 (58%) feeding tubes were confirmed in post-pyloric position on X-ray. Of these, two were in jejunal position (past the ligament of Treitz). Regarding post-pyloric feeding tube insertion in patients with delayed gastric emptying (GRV >500mL/24h) only one procedure was successful (25%). In patients who were administered prokinetics, this was 75% (n=3). In four patients (13%), there was disagreement between camera image and radiographic confirmation. Based on camera images, it was thought that the feeding tubes were in post-pyloric position, but on X-ray, they were not. Reasons for terminating the insertion procedure before reaching the post-pyloric position and leaving the tube in the gastric position included difficulties due to the absence of gastric peristalsis (n=1), inability to pass the pylorus (n=1), blurred image impairing evaluation of the tube position (n=2), an urgent need for non-invasive mask ventilation (desaturation SaO_2 <90% before start of procedure, n=1), discomfort of the patient (n=2), and suspected altered anatomy (n=1) (see **Table 3** and **Supplement 3**).

Table 2. Feeding tube placement procedure details

Feeding tubes inserted by operator 1	*N (%)*	15 (48)
Feeding tube diameter 10 Fr*	*N (%)*	12 (39)
Feeding tube length 140 cm**	*N (%)*	9 (29)
Number of attempts	*N (%)*	
1		17 (55)
2		8 (26)
3		5 (16)
4		1 (3)
Total procedure time (start-ready for use) [min]	*Median (IQR)*	64.0 (38.0-86.5)
Preparation time [min]	*Median (IQR)*	2.0 (1.6-3.0)
Time needed to insert (all tubes) [min] *(n=30)*	*Median (IQR)*	9.8 (4.8-28.3)
Time until X-ray [min] (incl examination, *n=30*)	*Median (IQR)*	43.5 (28.4-58.7)
Time needed to insert gastric tubes [min] *(n=12)*	*Median (IQR)*	15.6 (6.1-29.0)
Time needed to insert *post-pyloric* tubes [min] *(n=18)*	*Median (IQR)*	8.7 (4.7-28.1)
Time needed to insert jejunal tubes [min] *(n=2)*	*Mean (min-max)*	28.9 (27.4-30.4)

N = number; Fr = French; IQR = interquartile range; min = minutes; min-max = minimum-maximum;
** as compared to 12Fr feeding tubes; ** as compared to 109cm feeding tubes;*
NB: all tubes were attempted to be placed at the post-pyloric position.

Table 3. Outcomes and safety of the procedure

Postpyloric position achieved	*N (%)*	18 (58)
Bulbus duodeni	*N (%)*	8 (44)
Pars descendens	*N (%)*	1 (6)
Transitional part of the pars descendens/inferior	*N (%)*	5 (28)
Pars inferior	*N (%)*	2 (11)
Jejunal position	*N (%)*	2 (11)
Visualization of trachea	*N (%)*	8 (26)
Desaturation (SaO_2 < 90%)	*N (%)*	2 (7)
Airway tube migration	*N (%)*	1 (3)
Epistaxis	*N (%)*	1 (3)
Operator's evaluation score, overall (min. 3, max.14) (n=29)	*Median (IQR)*	9 (7-13)
Task difficulty (1=Very Difficult; 5=Very Easy)	*Median (IQR)*	3 (2-4)
Satisfaction with the device (1=Very Unsatisfied; 5=Very Satisfied)	*Median (IQR)*	4 (2-5)
Task time to achieve result (1=Too Much Time; 4=Very Little Time)	*Median (IQR)*	3 (2-4)

N = number; IQR = interquartile range; SaO_2 = plethysmographic arterial oxygen saturation; min. = minimum; max. = maximum.

Secondary outcomes: ease of use and safety parameters

The majority (n=17) of IRIS feeding tubes were placed on the first attempt. However, some insertions needed a second (n=8), third (n=5) or fourth attempt (n=1), mainly due to malposition in the trachea during the procedure (n=8). In two patients, tracheal visualization occurred twice.

Ten patients (32%) experienced adverse events; eight patients experienced adverse events that were considered unlikely or *un*related to IRIS feeding tube insertion (see **Supplement 2**). Two events were possibly related; in one patient, it was noticed on X-ray that the endotracheal tube had migrated into the right main bronchus after using a video laryngoscope to facilitate insertion of the IRIS feeding tube into the esophagus of a mechanically ventilated patient. Furthermore, one procedure was terminated due to significant bleeding (epistaxis) and desaturation.

Follow-up

The median duration of study participation was four days (range 1-30; **Table 4**). In total, 75 daily screenshots were taken to identify the correct position during enteral feeding. On the second and fourth day after insertion (study days three and five respectively), 2/18 and 2/4 screenshots were blurred, impairing evaluation of proper positioning (**Figure 2**).

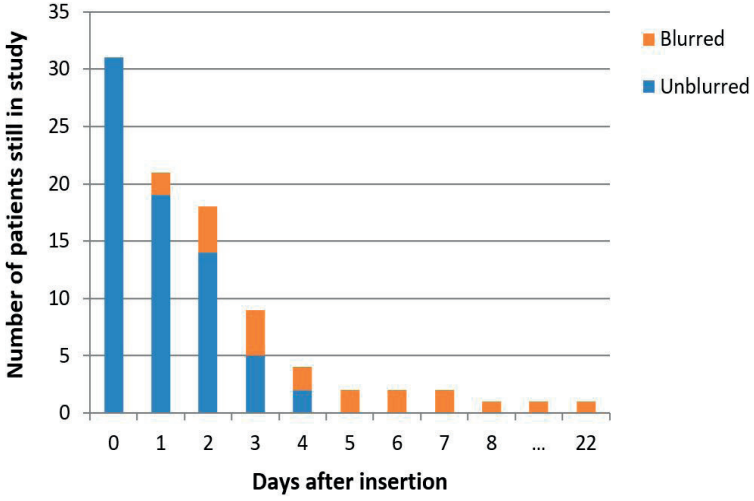
Nine patients (30%) were discharged to the general ward with the IRIS feeding tube in place. The most common reason for ending the study was the removal of the feeding tube by patients in a delirium (40%). One tube had to be removed due to cracked feeding ports resulting in enteral feeding leakage.

Table 4. Follow-up after IRIS technology feeding tube placement

		N=30
Number of screenshots per patient (total 75)	*Median (IQR)*	2 (0-3; range 0-22)
Number of study days (total 158 days)	*Median (IQR)*	4 (2-6; range 1-30)
Discharged with IRIS feeding tube to general ward	*N (%)*	9 (30)
Reason to terminate study	*N (%)*	
Insertion not successful		3 (10)
Removed by patient		12 (40)
Removed accidentally by healthcare provider		3 (10)
No longer an indication for feeding tube		9 (30)
Other reasons*		3 (10)

N = number; IQR = interquartile range;
**Other reasons to terminate the study:*
-Removal of feeding tube requested by patient and approved by ICU doctors (n=1)
-Transfer to another hospital (n=1)
-Leakage of the feeding tube (cracked port).

Figure 2. Visualization (daily screenshots) of gastric/duodenal mucosa with IRIS-technology



Daily screenshots were made to evaluate the feeding tube position and the ability of the IRIS-camera to visualize the gastric/duodenal mucosa over time. One tube had to be removed due to a cracked feeding port resulting in enteral feeding leakage.

Secondary outcome: feasibility

In total, 29 operator's questionnaires were filled out. The median total score (range 3-14) for overall evaluation composed of task difficulty, device, and task time, was 9 (IQR 7-13). Satisfaction with the device scored median four on a 5-point Likert scale (IQR 2-5). The degree of satisfaction was highly correlated with successful post-pyloric placement (p=0.005).

Secondary outcome: procedural time

One operator at a time performed the procedure. The total procedure time (defined as the time from start preparations until ready for use) for all feeding tubes was median 64.0 minutes (IQR 38.0-86.5). This period was composed of preparation time (median 2.0 minutes; IQR 1.6-3.0), the time needed for proper feeding tube insertion in post-pyloric position (median 8.7 minutes (IQR 4.7-28.1)) and waiting time until X-ray confirmation (median 43.5 minutes (IQR 28.4-58.7)).

Patients' evaluation

No patient questionnaires were completed; most patients were delirious (n=20) or unconscious (n=9) during tube insertion. Two patients who were conscious during placement were sedated and mechanically ventilated within 24 hours after tube placement.

Discussion

Using Integrated Real-Time Imaging, about 58% of feeding tubes were successfully placed in the post-pyloric position, and 96.8% were properly placed when gastric placement should have been the goal. To achieve this success percentage, tube placements were limited to two trained physicians to guarantee a high exposure, and after a training session of 5 placements.

To date, this is the most extensive series of feeding tubes using IRIS-technology placed in the post-pyloric position. Mizzi *et al.* (2017) successfully inserted feeding tubes in the lower third of the stomach in 20 patients in a neurological ICU using IRIS-technology (28). The correct position was confirmed by X-ray. Wischmeyer *et al.* (2019) demonstrated proper IRIS feeding tube placement in 44 of 45 ICU patients (97.8%), of which 6.8% were inserted post-pyloric (27). Regarding tracheal visualization, an incidence of 27% was reported in our study. Notably, this was higher than Wischmeyer (20%) but lower than Mizzi (35%) (27,28). This might be explained by the number of patients on mechanical ventilation: 42% and 95% respectively versus 45% in our study. In all three studies, image quality of screenshots declined as the camera became obscured during the

follow-up period, impairing proper evaluation of the feeding tube position. We also reported problems with image quality during the feeding tube insertion. A blurred vision hampered two procedures; air insufflation did not improve the situation, making proper visual confirmation impossible.

Moreover, we reported disagreement between the camera image and radiographic confirmation in four patients (12.5%). Based on camera images, it was thought that the feeding tubes were in post-pyloric position, but on X-ray, they were not. This may be due to insufficient camera image quality or user experience. A similar situation was reported by Wischmeyer *et al.* who attributed this to feeding tube migration after insertion (27). In our study, in all four cases 109cm tubes were used. These tubes precluded deeper placement compared to the 140cm feeding tubes, which may have contributed to migration back into the gastric space. In addition to this, many critically ill ICU patients have reduced gastric motility and suffer from retroperistalsis, further hampering post-pyloric tube positioning (11). In the current study, only 25% of insertions was successful in patients with delayed gastric emptying, which increased to 75% when prokinetics were administered. IRIS technology is therefore – unless further developed – at present not suitable for post-pyloric tube positioning in this patient category.

Regarding nasojejunal placement, the IRIS technique performed poorly (only 7%) with a mean procedure time of 28.9 minutes, due to a lack of anatomical markers on the exact position in the duodenum and the flexibility of the tube hampering passing the tube to a deep post-pyloric position.

Comparison of the Integrated Real-Time Imaging technique with Cortrak, fluoroscopy and endoscopy

Two systematic reviews by Gerritsen *et al.* (2015) and Wei *et al.* (2020) reported success rates of Cortrak and endoscopy to be about 82.6-85% and 83.1-89% respectively, and 93% for fluoroscopy (10,34). This is in contrast with 58% for IRIS technology. It should be noted however, that both reviews defined success as "tip of the tube in the post-pyloric position". By this definition, 22 (73%) of IRIS tubes were successfully placed post-pyloric.

Gerritsen *et al.* reported procedural times of 13.4 (SD 12.9, 16.2 (SD 23.6) and 14.9 (SD 8.7) minutes, for Cortrak, fluoroscopy and endoscopy respectively (10,12,13,21,24,35,36). The time needed for post-pyloric procedures using the IRIS technology (mean 14.2 (SD 13.1) minutes) was comparable to these methods (10). Of note, we reported an additional median waiting time of 43.5 minutes for X-Ray confirmation, which is not necessary after Cortrak or endoscopic placement. Other studies have reported waiting times up to 78.8 minutes for radiography (20).

In terms of clinical workflow, compared with the electromagnetic Cortrak technique, with IRIS feeding tubes there is no need to exclude patients with medical implants affected by electromagnetic fields (26). Compared to endoscopic procedures, IRIS guided placement can be performed with less sedation. Only a third of the study participants who were conscious during feeding tube insertion were administered midazolam periprocedurally. Moreover, IRIS guided insertion may avoid time-consuming scheduling with different departments and – in some hospitals – removes the risk associated with transporting critically ill patients through the hospital (3,13). In our study, feeding tubes were inserted immediately, whenever the study team was available. There was no need to wait for an endoscopy team, making the shortening procedure time and less demanding on personnel. In our hospital, Cortrak and endoscopically placed feeding tubes are commonly not inserted during weekends and holidays. Patients who need these interventions must wait until the next working day, which causes considerable feeding delays. In the literature, delays of up to 7.5 hours until initiation of feeding translated into a mean caloric deficit of 850 kilocalories (3,25,35). After the failure of initial electromagnetically guided placement, this delay may increase to an average of 17 hours before a feeding tube is inserted endoscopically or radiologically (3). Although not investigated in this study, similar delays with the IRIS-technology could be expected. However, the time until the first attempt was much shorter than 7 hours in our study. Finally, if feeding tube migration is suspected, IRIS feeding tube position can be checked at the bedside if the camera is not blurred (27,28). Like Cortrak feeding tubes, it is possible to rewire and reposition the tube, whereas endoscopically placed tubes that migrate would necessitate the removal of the tube and replacement in a new procedure (36).

X-Ray confirmation

For the future, when camera image quality is improved to make better distinction of the antrum-pylorus-duodenum, IRIS technology will make X-rays redundant to conform proper post-pyloric placement. Artificial intelligence techniques for processing and analysis of images may further enhance this. X-ray confirmation is no longer necessary when gastric placement is the goal. In this study, there was 100% agreement between X-ray and real-time imaging regarding placement in the gastrointestinal tract. None of the feeding tubes positioned in the stomach, duodenum or jejunum using IRIS guidance was found to be in the respiratory tract on X-ray. Hemington-Gorse *et al.* (2011) calculated that a chest or abdominal film dose is similar to 10 days or 2-3 years of background radiation, respectively (25). Using IRIS technology, enteral nutrition can be safely started immediately after tube insertion.

Safety

An important finding in this study was the avoidance of airway placement in 27% of all patients. Due to real-time visualization of anatomic landmarks, entering the trachea was immediately recognized and corrected early in the procedure. In contrast, in one patient the insertion procedure was discontinued due to epistaxis with oxygen desaturation (0.03%), and in another patient airway tube migration was encountered after using a video laryngoscope to introduce the feeding tube. In both cases, the slightly larger diameter of the IRIS feeding tube tip (containing the camera) might have contributed to these observations. In current literature, placement-related epistaxis was reported 3.5% and 4.8% in the Cortrak and endosopic insertions respectively. With respect to procedure-associated hypoxia, this was 0.3% and 1.6% respectively (34). The use of periprocedural sedative medication and the larger diameter of the endoscope may account for this difference in reported insertion-related desaturations.

Costs

The IRIS console acquisition costs are estimated at €2,500 for the console and €125 per consumable post-pyloric feeding tube. For Cortrak technology, estimated prices are €13,500 for the console and €115 for corresponding tubes (26). Conventional post-pyloric feeding tubes are less expensive (€78) but incur additional costs for (repeated) radiographic or alternative confirmation of the correct position (26). Roberts *et al*. (2007), stated that a single fatal event due to mispositioning of a feeding tube is disastrous and therefore can justify alternative and safer methods for feeding tube insertions, although acquisition costs may be higher (14,18). Like the Cortrak method, IRIS-guided insertion reduces staffing workload and avoids patient transportation through the hospital. The associated cost reduction is estimated to be as much as €1,100 per attempt (13).

Strengths

Strengths of this study include the number of post-pyloric and nasojejunal feeding tubes compared to previous studies, and daily follow-up until 30 days. Moreover, blind evaluation of chest and upper abdominal X-rays increased the reliability of tube positioning.

Limitations

Although this is the most extensive study with IRIS feeding tubes in post-pyloric position, it is limited by its single-centre and no comparison design, and only two trained physicians performing the procedures. Suggestions for further research include the success rates of IRIS feeding tube insertion in patients with an indication for nasojejunal feeding tubes. When studying patients with gastroparesis, routinely administration of prokinetics might be added or a (magnetic) technique to move the tip of the feeding tube (mini-endoscope) to make the device more suitable for post-pyloric placement.

Moreover, image quality should be improved. Finally, a study reporting accurate cost-effectiveness analyses of the IRIS technology feeding tubes is recommended, as well as a cost comparison study of all three abovementioned methods.

Conclusion

This study showed that real-time video-assisted placement of upper gastrointestinal feeding tubes in critically ill ICU patients using the IRIS-technology had a success rate of 58% for post-pyloric placement and a 96.8% for gastric placement. However, deep jejunal placement was achieved in only a low number of attempts. The technique is safe in avoiding tracheal malpositioning. When camera image quality is improved, this method will be more suitable for post-pyloric placement and can make X-rays redundant. Furthermore, this technique allows daily checks for correct positioning, thereby minimizing the risk of tube migration and aspiration, although the image quality declines after two days.

References

1. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019 Feb;38(1):48-79.
2. Singer P, Elia L. Technology innovations in delivering accurate nutrition. ICU Manag Pract 2019;19(1):25-28.
3. Kaffarnik MF, Lock JF, Wassilew G, Neuhaus P. The use of bedside electromagnetically guided nasointestinal tube for jejunal feeding of critical ill surgical patients. Technol Health Care. 2013;21(1):1-8.
4. Alkhawaja S, Martin C, Butler RJ, Gwadry-Sridhar F. Post-pyloric versus gastric tube feeding for preventing pneumonia and improving nutritional outcomes in critically ill adults. Cochrane Database Syst Rev. 2015 Aug 4;2015(8):CD008875.
5. August DA, Huhmann MB; American Society for Parenteral and Enteral Nutrition (ASPEN) Board of Directors. ASPEN clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr. 2009 Sep-Oct;33(5):472-500.
6. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003 Sep-Oct;27(5):355-73.
7. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al; ESICM Working Group on Gastrointestinal Function. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017 Feb 6;43(3):380-398.
8. Davies AR, Morrison SS, Bailey MJ, Bellomo R, Cooper DJ, Doig GS, et al. ENTERIC Study Investigators; ANZICS Clinical Trials Group. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. Crit Care Med 2012 Aug;40(8):2342-8.
9. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211.
10. Gerritsen A, van der Poel MJ, de Rooij T, Molenaar IQ, Bergman JJ, Busch OR, et al. Systematic review on bedside electromagnetic-guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes. Gastrointest Endosc 2015 Apr;81(4):836-47.
11. Silk DB. The evolving role of post-ligament of Trietz nasojejunal feeding in enteral nutrition and the need for improved feeding tube design and placement methods. JPEN J Parenter Enteral Nutr. 2011 May;35(3):303-7.
12. Holzinger U, Brunner R, Miehsler W, Herkner H, Kitzberger R, Fuhrmann V, et al. Jejunal tube placement in critically ill patients: A prospective, randomized trial comparing the endoscopic technique with the electromagnetically visualized method. Crit Care Med. 2011 Jan;39(1):73-7.
13. Gerritsen A, de Rooij T, Dijkgraaf MG, Busch OR, Bergman JJ, Ubbink DT, et al. Electromagnetic-Guided Bedside Placement of Nasoenteral Feeding Tubes by Nurses Is Non-Inferior to Endoscopic Placement by Gastroenterologists: A Multicenter Randomized Controlled Trial. Am J Gastroenterol. 2016 Aug;111(8):1123-32.

14. Sparks DA, Chase DM, Coughlin LM, Perry E. Pulmonary complications of 9931 narrow-bore nasoenteric tubes during blind placement: a critical review. JPEN J Parenter Enteral Nutr. 2011 Sep;35(5):625-9.
15. Rassias AJ, Ball PA, Corwin HL. A prospective study of tracheopulmonary complications associated with the placement of narrow-bore enteral feeding tubes. Crit Care. 1998;2(1):25-28.
16. Haas LE, Tjan DH, van Zanten AR. 'Nutrothorax' due to misplacement of a nasogastric feeding tube. Neth J Med. 2006 Nov;64(10):385-6.
17. Metheny NA, Titler MG. Assessing placement of feeding tubes. Am J Nurs. 2001 May;101(5):36-45.
18. Roberts S, Echeverria P, Gabriel SA. Devices and techniques for bedside enteral feeding tube placement. Nutr Clin Pract. 2007 Aug;22(4):412-20.
19. Halloran O, Grecu B, Sinha A. Methods and complications of nasoenteral intubation. JPEN J Parenter Enteral Nutr. 2011 Jan;35(1):61-6.
20. Powers J, Fischer MH, Ziemba-Davis M, Brown J, Phillips DM. Elimination of radiographic confirmation for small-bowel feeding tubes in critical care. Am J Crit Care. 2013 Nov;22(6):521-7.
21. Powers J, Luebbehusen M, Spitzer T, Coddington A, Beeson T, Brown J, et al. Verification of an electromagnetic placement device compared with abdominal radiograph to predict accuracy of feeding tube placement. JPEN J Parenter Enteral Nutr. 2011 Jul;35(4):535-9.
22. Lamont T, Beaumont C, Fayaz A, Healey F, Huehns T, Law R, et al. Checking placement of nasogastric feeding tubes in adults (interpretation of x ray images): summary of a safety report from the National Patient Safety Agency. BMJ. 2011 May 5;342:d2586.
23. Patient Safety Alert NPSA/2011/PSA002: Reducing the harm caused by misplaced nasogastric feeding tubes in adults, children and infants. United Kingdom: National Patient Safety Agency, 2011. (Accessed November 14, 2020, at http://www.gbukenteral.com/pdf/NPSA-Alert-2011.pdf).
24. Taylor S, Allan K, McWilliam H, Manara A, Brown J, Toher D, et al. Confirming nasogastric tube position with electromagnetic tracking versus pH or X-ray and tube radio-opacity. Br J Nurs. 2014 Apr 10-23;23(7):352, 354-8.
25. Hemington-Gorse SJ, Sheppard NN, Martin R, Shelley O, Philp B, Dziewulski P. The use of the Cortrak Enteral Access System™ for post-pyloric (PP) feeding tube placement in a Burns Intensive care unit. Burns. 2011 Mar;37(2):277-80
26. CORTRAK 2 Enteral Access System for placing nasoenteral feeding tubes. Medtech innovation briefing. United Kingdom: National Institute for Health and Care Excellence (NICE), 2016. (Accessed November 14, 2020, at nice.org.uk/guidance/mib48).
27. Wischmeyer PE, McMoon MM, Waldron NH, Dye EJ. Successful Identification of Anatomical Markers and Placement of Feeding Tubes in Critically Ill Patients via Camera-Assisted Technology with Real-Time Video Guidance. JPEN J Parenter Enteral Nutr. 2019 Jan;43(1):118-125.
28. Mizzi A, Cozzi S, Beretta L, Greco M, Braga M. Real-time image-guided nasogastric feeding tube placement: A case series using Kangaroo with IRIS Technology in an ICU. Nutrition. 2017 May;37:48-52.
29. Sauro J, Kindlund E. A Method to Standardize Usability Metrics Into a Single Score. Proc SIGCHI Conf Hum Factor Comput Syst 2005 Apr;401-409.
30. Sjetne IS, Bjertnaes OA, Olsen RV, Iversen HH, Bukholm G. The Generic Short Patient Experiences Questionnaire (GS-PEQ): identification of core items from a survey in Norway. BMC Health Serv Res. 2011 Apr 21;11:88.

31. Yacavone RF, Locke GR 3rd, Gostout CJ, Rockwood TH, Thieling S, Zinsmeister AR. Factors influencing patient satisfaction with GI endoscopy. Gastrointest Endosc. 2001 Jun;53(7):703-10.
32. P Pettersen KI, Veenstra M, Guldvog B, Kolstad A. The Patient Experiences Questionnaire: development, validity and reliability. Int J Qual Health Care. 2004 Dec;16(6):453-63.
33. Nijjar UK, Edwards JA, Short MW. Patient satisfaction with family physician colonoscopists. J Am Board Fam Med. 2011 Jan-Feb;24(1):51-6.
34. Wei Y, Jin Z, Zhu Y, Hu W. Electromagnetic-guided versus endoscopic placement of post-pyloric feeding tubes: a systematic review and meta-analysis of randomised controlled trials. J Intensive Care. 2020 Dec 10;8(1):92.
35. Wang X, Zhang L, Wu C, Li N, Li J. The application of electromagnetically guided post-pyloric feeding tube placement in critically ill patients. J Invest Surg. 2014 Feb;27(1):21-6.
36. Kappelle WFW, Walter D, Stadhouders PH, Jebbink HJA, Vleggaar FP, van der Schaar PJ, et al. Electromagnetic-guided placement of nasoduodenal feeding tubes versus endoscopic placement: a randomized, multicenter trial. Gastrointest Endosc. 2018 Jan;87(1):110-118.

Supplemental material

Supplement 1. Evaluation operator and patient

A. Questionnaire for operators' evaluation

1. Completion Rate

1=Task success (=post-pyloric position of feeding tube on X-Ray); 0=Task failure

Number of attempts: ….

2. Usability problems

Did you encounter any problems in using the Kangaroo feeding tube? Y/N

If yes, describe the problem

……

3. Task time

How long did it take to insert a feeding tube [in minutes]?

….. minutes

4. Task level satisfaction (difficulty task) – Single Usability Metric (SUM)

A. How difficult / easy was it to complete this task?

Very Difficult				Very Easy
1	2	3	4	5

B. How satisfied are you with using this application to complete this task?

Very Unsatisfied				Very Satisfied
1	2	3	4	5

C. How would you rate the amount of time it took to insert the feeding tube?

Too Much Time				Very Little Time
1	2	3	4	5

B. Questionnaire for patients' evaluation

1. Did you have a previous experience of enteral feeding tube placement? Y/N

		Excellent	Very Good	Good	Fair	Poor
2	Was the procedure explained to you properly?					
3	Were the instructions during the procedure understandable and clear?					
4	Were you satisfied with the help provided by the physician and/or nurses during the procedure?					
5	How did you find the attitude of the physician/ nurse who performed the procedure?					
6	Please rank the technical skills of the physician/ nurse who inserted the feeding tube					
7	How did you find the attitude of the nurses and other support staff?					

8. Please assess the level of discomfort during the procedure

☐ No discomfort at all
☐ Slight discomfort
☐ Mild discomfort
☐ Moderate discomfort
☐ Severe discomfort

9. Please assess your experience with the insertion of a feeding tube

☐ Very Negative
☐ Negative
☐ Nothing special
☐ Positive

10. Would you be willing to undergo this procedure again when necessary?

☐ Yes
☐ Yes, but with another doctor
☐ Partly
☐ No

Supplement 2. Study adverse events

	N (%)	Possibly related	Unlikely related	Unrelated
Uneventful	20 (65)	NA	NA	NA
Visualisation of the trachea	8 (26)	0	8	0
Desaturation (SaO_2 <90%)	2 (6)	1	0	1
Airway tube migration	1 (3)	1	0	0
Epistaxis	1 (3)	1	0	0
Infectious complication	8 (26)	0	0	8
Vascular event (thrombosis, ischemia)	2 (6)	0	0	2
ICU acquired weakness	2 (6)	0	0	2
Readmission to the ICU	1 (3)	0	0	1

N = number; NA = not applicable; SaO_2 = plethysmographic arterial oxygen saturation; ICU = intensive care unit.
NB: In some cases, two or more events were reported, therefore numbers do not add up to 31.

Supplement 3. Reported (usability) problems

	N (%)	(Possibly) related	Unlikely related	Unrelated
None	17 (55)	NA	NA	NA
Unsafe swallowing function	1 (3)	0	0	1
Difficulty to reach post-pyloric position	9 (29)	6	0	3
Absence of gastric peristalsis	1 (11)	0	0	1
Blurred camera image	2 (22)	2	0	0
Inability to pass the pylorus	1 (11)	1	0	0
Urgent need for non-invasive mask ventilation	1 (11)	0	0	1
Discomfort, need for additional sedation	3 (33)	3	0	0
Suspected altered anatomy	1 (11)	0	0	1
Disagreement between camera and X-ray imaging	4 (13)	4	0	0

N = number; NA = not applicable.
NB: In some cases, two or more events were reported, therefore numbers do not add up to 31.

CHAPTER 4

Refeeding syndrome: relevance for the critically ill patient

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Abstract

Purpose of review

To provide an overview of recent findings concerning refeeding syndrome (RFS) among critically ill patients and recommendations for daily practice.

Recent findings

Recent literature shows that RFS is common among critically ill ventilated patients. Usual risk factors for non-ICU patients addressed on ICU admission do not identify patients developing RFS. A marked drop of phosphate levels (>0.16 mmol/l) from normal levels within 72 hours of commencement of feeding, selects patients that benefit from hypocaloric or restricted caloric intake for at least 48 hours resulting in lower long-term mortality.

Summary

Refeeding syndrome is a potentially life-threatening condition induced by initiation of feeding after a period of starvation. Although a uniform definition is lacking, most definitions comprise a complex constellation of laboratory markers (i.e., hypophosphatemia, hypokalemia, hypomagnesemia) or clinical symptoms, including cardiac and pulmonary failure.

Recent studies show that low caloric intake results in lower mortality rates in critically ill RFS patients compared with RFS patients on full nutritional support. Therefore, standard monitoring of RFS-markers (especially serum phosphate) and caloric restriction when RFS is diagnosed should be considered. Furthermore, standard therapy with thiamin and electrolyte supplementation is essential.

Introduction

Refeeding syndrome (RFS) is associated with reintroduction of oral or (par)enteral feeding after deprivation of caloric intake, either acute or chronic (1–3). Burgers first described it in 1948 in liberated prisoners who were fed again after a period of starvation. These soldiers were advised a conservative caloric intake, to prevent gastrointestinal, pulmonary or cardiac complications, such as abdominal distension and diarrhea, dyspnea and pulmonary edema, tachycardia and heart failure (4–6). Despite an adequate nutritional intake, mortality of about 20% was observed (4,5).

Although it was described for the first time more than 70 years ago, refeeding syndrome and its relevance in critical illness remains unclear. This issue is mainly caused by the lack of a uniform RFS definition. However, regardless of the definition used, RFS is associated with significant morbidity and mortality, and therefore highly relevant in daily clinical practice (7,8). This narrative review aims to summarize what is currently known on this topic, focusing on the latest acquired insights.

Definition of refeeding syndrome

Standard definitions of RFS are hallmarked by hypophosphatemia, combined with low concentrations of serum magnesium and potassium. This may lead – if untreated – to gastrointestinal, pulmonary or cardiac complications. Other symptoms may include sodium and fluid imbalances, thiamine (vitamin B1) deficiency as well as changes in protein, glucose and fat metabolism including insulin resistance (1). A general definition with clear cut-off points of RFS is lacking, making a comprehensive study on this topic confusing. Furthermore, specific data on critically ill patients is scarce. In a recent systematic review conducted by Friedli *et al.* only 38 of the 45 included studies reported an RFS definition, all being highly heterogeneous (6). Some definitions were only based on electrolyte disturbances with different cut-off values, while other studies also included clinical symptoms. Most commonly used definitions were based on hypophosphatemia, with cut-off values ranging from 0.32 mmol/L to 1 mmol/L, and/or a fall from baseline greater than 30% or more than 0.16 mmol/L (6).

Epidemiology

Due to different definitions, the actual incidence of RFS remains unknown in both critically ill and non-critically ill (i.e., anorexia nervosa) patients. In the systematic review conducted by Friedly *et al.*, eleven of 32 studies reported an incidence of zero

percent (6). This may be caused by narrow definitions of RFS used. Furthermore, studies were performed among heterogeneous patient groups. Other studies using broader definitions, reported RFS incidences up to 80%, mainly occurring in the first 72 hours after the start of nutritional support. In a prospective cohort study conducted by Rio *et al.*, a so-called three-facet criteria design was used to confirm the diagnosis of RFS unequivocally. These criteria comprised disturbed electrolyte balances, acute peripheral edema or circulatory fluid overload combined with disturbances in organ function. According to these criteria, an incidence rate of only two percent was reported (n=3) (8,9).

In critically ill patients, refeeding syndrome is most often defined by the occurrence of electrolyte disturbances (mainly hypophosphatemia) within 72 hours of the initiation of feeding, not attributed to other causes. The incidence of refeeding hypophosphatemia is reported to be 34-52% in critical illness (10–12).

Outcomes of patients with refeeding syndrome

Friedli *et al*. noticed that only eleven studies reported on outcomes in RFS patients versus non-RFS patients. Although lacking methodological quality, four studies described more extended hospital stays and five studies reported higher mortality rates in the RFS patient groups (6).

Recently, Matthews *et al*. studied the prevalence rate of RFS as a cause of death (9). They conducted a retrospective observational study amongst patients who passed away in Queensland hospitals (Australia) between 1997 and 2015 not exclusively treated in Intensive Care Units (ICUs). Over these eighteen years, approximately 260,000 patients died; however, only five patients had RFS as an underlying cause of death mentioned on their official death certificates. All but one were assessed as being at risk for RFS on admission. In none of these patients, RFS was the primary cause of death (mortality rate 0%).

However, when focusing on critically ill patients, Olthof and coworkers performed a retrospective study amongst exclusively mechanically ventilated (>7 days) patients at a mixed medical-surgical ICU (10). A total of 337 patients were enrolled in this study, of whom 124 (36.8%) developed RFS. No statistical significance in length of hospital stay was observed between both groups. Concerning long-term outcomes, no difference in six-month mortality was observed (33.9% in RFS and 31.5% in non-RFS, p=0.65). This is in contrast with results published by Coskun *et al*. who reported significant differences in length of hospital stay (p=0.025) and mortality rates (p=0.037), both in favor of patients without RFS (11). However, this may be due to different cut-off values

of hypophosphatemia, as well as the fact that Coskun e*t al.* included many patients with comorbidities (70%) and malignant diseases (20%). On the other hand, mortality rates found in patients with anorexia nervosa and other severe malnutritional states, have been reported at 10-29%, although it can be questioned whether these deaths should be primarily attributed to RFS (13,14).

Although it is debatable whether RFS is directly correlated with mortality, there is evidence that appropriate treatment – as will be described later – will ultimately lead to better overall survival. Therefore it is highly relevant to identify individuals at risk appropriately.

Pathophysiology

To date, the pathophysiology of RFS is not entirely understood. The metabolic derangements following the reintroduction of feeding include hormonal and electrolyte disturbances..

Metabolic changes during starvation

In normal circumstances, the primary fuel of the body consists of glucose, derived from carbohydrate breakdown. At least 100-150 grams of glucose is needed daily for optimal brain function, and to prevent protein breakdown (3). Excess of carbohydrate and protein intake can be stored as fat.

During a short period of fasting (up to 24 hours), glycogen – which is stored in the liver and muscles – can be utilized after glycogenolysis to provide glucose. During prolonged fasting, metabolism switches to fat and protein utilization after the glycogen stores have been depleted. Glucose is produced by degradation of amino acids, fatty acids, lactate, and pyruvate through gluconeogenesis (3,15). When the fasting period prolongs, the metabolic rate decreases by 20-25% (1,3). Concomitantly, intracellular electrolytes and vitamin supplies are depleted (3,6,7).

Metabolic changes and clinical symptoms during refeeding

When a refeeding programme is started, whether oral or (par)enteral, metabolism switches back from protein and fat metabolism to the breakdown of carbohydrates (1–3). This results in a marked increase in insulin secretion, leading to increased

intracellular uptake of glucose, but also of electrolytes such as phosphate, potassium, and magnesium. This shift, along with already depleted electrolyte storages, may lead to dangerously low electrolyte concentrations (3). Simultaneously, insulin resistance is observed – marked by the coexistence of hyperinsulinemia and hyperglycemia – resulting in increased sodium and water retention, most likely due to an antinatriuretic effect of insulin on the renal tubules (3). This may result in extracellular volume expansion, leading to peripheral edema and – if severe enough – to heart failure and pulmonary edema (1,6). Transcellular shifts and redistributions of electrolytes may result in cardiac (arrhythmia), neuromuscular (muscle weakness, spasms, rhabdomyolysis) and hematopoietic (anemia, reduced oxygen supply) impairment, finally leading to organ dysfunction, organ failure and ultimately death if not appropriately treated (6,10,15). Many clinical signs and symptoms of RFS are indistinguishable from multiple organ dysfunction syndrome, complicating the diagnosis (7).

The outcome of refeeding syndrome during critical illness related to nutrition support

In a recent retrospective cohort study, Olthof and co-workers describe the effect of (hypo)caloric intake on outcome in critically ill mechanically ventilated patients during refeeding hypophosphatemia (10). They observed no statistical differences in clinical outcomes between the RFS and non-RFS patients groups. However, within the RFS population, reduced six-month mortality was observed in the patients who were treated with hypocaloric intake (<50% of calculated target) compared with patients who received higher amounts of calories (adjusted hazard ratio 0.39, 95% CI 0.16-0.95%, p=0.037). At day 180 after ICU admission, lower caloric intake during RFS was associated with an increased overall survival.

This is consistent with findings by Doig *et al*. who in a randomized controlled trial comparing standard versus restricted caloric intake (<500 kcal/day) in critically ill RFS patients identified by refeeding hypophosphatemia, who were mechanically ventilated (16). They observed that the full caloric strategy was associated with higher mortality rates at 60 and 90 days post-hospitalization.

In the studies by Olthof and Doig the Kaplan-Meier survival curves do not separate RFS patients with low caloric intake or caloric restriction from patients on full support during the early phase of the emergence of electrolyte abnormalities and the RFS diagnosis (10,16). However, mortality rates seem to separate from two weeks after the diagnosis, suggesting that not the acute electrolyte abnormalities play a significant role, but the metabolic consequences of RFS are more critical. The exact mechanism of these observations warrants further research.

Electrolyte changes during refeeding syndrome

Phosphate

Phosphate is essential for the structural integrity of the cell membrane. Moreover, it is an essential mineral for several intracellular processes, such as glucose metabolism and energy storage (adenosine triphosphate, ATP), as well as the activation of enzymes and second messengers (1,6). Hypophosphatemia is associated with impaired glucose tolerance and insulin resistance (15). Furthermore, phosphate regulates the affinity of hemoglobin for oxygen. Hypophosphatemia results in lowered levels of 2,3 diphosphoglyceride, resulting in an impaired oxygen release to peripheral tissues (3).

Potassium

Potassium is essential in maintaining the electrochemical membrane potential. When derangements occur, this may lead to cardiac arrhythmias and ultimately cardiac arrest (1,6).

Magnesium

Just like phosphate, magnesium depletion is associated with insulin resistance and impairment of glucose tolerance (15). Furthermore, magnesium is necessary for the structural integrity of ribosomes, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and plays an essential cofactor role in most enzyme systems, including the production of ATP. Moreover, magnesium is – like potassium – essential for maintaining the electromechanical membrane potential. When magnesium is depleted, this may result in cardiac and neuromuscular dysfunction (1,6,15).

Vitamin deficiency

All vitamins may become depleted during starvation, but the water-soluble thiamine (vitamin B1) has been considered – until now – the most important vitamin to become deficient as a consequence of RFS. Thiamine is an essential coenzyme for three enzymes in the glucose metabolism. When thiamine is deficient, the conversion of pyruvate to acetyl coenzyme-A (CoA) is impossible, resulting in lactate overproduction and lactic acidosis. It is also crucial in preventing Wernicke's encephalopathy or Korsakoff's syndrome (1,3). During the administration of carbohydrates during refeeding after starvation thiamine needs may increase and thiamine deficiency may become clinically relevant.

Risk factors for refeeding syndrome

Risk factors for RFS have been described in the guidelines of the National Institute for Health and Care Excellence (NICE), and include: low body mass index and/or unintentional weight loss within the last six months, a negligible food intake for more than 5 days, low electrolyte (phosphate, potassium, magnesium) levels prior to nutritional support, poor absorptive capacity, catabolism and chronic alcoholism (17). Other risk factors not mentioned in these guidelines include age (>70 years), low (pre) albumin or insulin-like growth factor, overfeeding, intravenous glucose infusion before nutritional support, or scoring ≥ 3 points on the nutritional risk screening (6,8,18). Rio *et al.* reported a sensitivity and specificity of these risk factors of 67% and >59% respectively (8). Only low baseline serum magnesium levels were able to predict RFS independently (p=0.021); other independent risk factors were non-significant. In daily practice, it may be hard to identify critically ill patients based on these criteria as electrolyte differences between RFS and non-RFS patients are small (10,19). Remarkably, in this study conducted by Rio *et al.*, only three of the 133 (2.3%) patients who were at risk, were diagnosed with RFS (8).

Utilizing universal preventive strategies based on risk scoring systems, such as electrolyte and thiamine supplementation, and hypocaloric refeeding schemes may then result in unnecessary delays until adequate nutritional support to malnourished patients (8,9). Therefore, it is essential to know whether critically ill patients should be treated with caloric restriction or not.

Identification, diagnosis, and treatment of refeeding syndrome in the ICU

In the studies by Doig and Olthof refeeding hypophosphatemia was used to identify patients with RFS (10,16). In both studies, most patients also showed other diagnostic RFS criteria such as hypomagnesemia and hypokalemia. In the Olthof study, RFS patients needed more phosphate, potassium and insulin supplementation suggesting that refeeding hypophosphatemia identifies patients with more signs and symptoms of RFS. Moreover, the outcome of patients in both the Doig and Olthof studies were influenced by low caloric intake or caloric restriction. As in the Olthof study, no suggested clinical risk factor was able to identify RFS patients on ICU admission with enough accuracy, phosphate monitoring seems the only way to separate patients with RFS from those without RFS (**Table 1**)(10).

Table 1. Identification of critically ill patients at risk for refeeding syndrome

Daily monitoring of serum phosphate and other electrolytes such as potassium, magnesium, especially during the first 72 hours after the start of nutritional support, irrespective of the route of feeding used
A decrease of serum phosphate levels of at least 0.16 mmol/L to below 0.65 mmol/L from normal levels on ICU admission within 72 hours after the commencement of nutrition after excluding other causes of hypophosphatemia (Refeeding Hypophosphatemia) is suggestive for Refeeding Syndrome
Among reasons not to classify patients as having refeeding hypophosphatemia or Refeeding Syndrome based on low serum phosphate levels are ongoing renal replacement therapy, recent parathyroidectomy, or pharmacologic treatment for hyperphosphatemia

As common risk factors fail to identify RFS patients, regular phosphate and other electrolyte monitoring can be recommended at least once daily, in particular during the first 72 hours after the initiation of nutritional support (see **Table 1**)(1,9,10).

Standard treatment of RFS comprises electrolyte supplementation, insulin therapy in case of hyperglycemia, volume correction if necessary, and vitamin supplementation in particular vitamin B1 (see **Table 2**).

Table 2. Treatment strategies for critically ill patients with refeeding hypophosphatemia and refeeding syndrome

Electrolyte supplementation (phosphate, magnesium, potassium)
Glucose monitoring to prevent hypoglycemia and hyperglycemia
Intravenous insulin administration in case of hyperglycemia
Correction of fluid overload if necessary
Thiamine supplementation at a minimum dose of 100mg daily, for at least 7-10 days
Restriction of total caloric intake to a maximum of 500 kcal/24 hours during the first 48 hours after the diagnosis of Refeeding Hypophosphatemia and Refeeding Syndrome
Consider the amount of non-nutritional calories from propofol, citrate (renal replacement therapy) and intravenous carbohydrate solutions as these may increase the total caloric load
Gradually advance feeding after 48 hours of caloric restriction in daily steps of 25% of the target until the nutrition target is reached

Based on the recent observations by Doig and Olthof caloric intake restriction at 500 kcal/24 hours for 48 hours can be recommended (10,16). It is essential to include additional sources of caloric intake (non-nutritional calories) in total caloric intake calculations, such as propofol infusion and citrate administration from renal replacement therapy, as in individual patients these non-nutritional calories may be even higher than this arbitrary cut-off for caloric restriction (20).

Since glucose intake followed by insulin secretion is the primary trigger for RFS, restricted nutritional intake should be accompanied by adequate glucose control to prevent both hyperglycemia and hypoglycemia (3).

Conclusions

Refeeding syndrome is a potentially life-threatening condition caused by metabolic, endocrine and electrolyte derangements induced by the initiation of feeding after a period of starvation. Although a uniform definition is lacking, for critically ill patients phosphate monitoring after the start of nutritional support for at least 72 hours seems the most straightforward method to identify patients with refeeding syndrome as refeeding hypophosphatemia best identifies such patients. Immediate supplementation of electrolytes, vitamin B1 and - if necessary - insulin is warranted. However, also marked caloric restriction for several days can be recommended during critical illness as this nutritional strategy has been shown to be associated with improved long-term outcomes. After this restriction period gradually advancing to nutritional targets can be performed.

References

1. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008 Jun 28;336(7659):1495-8.
2. Zeki S, Culkin A, Gabe SM, Nightingale JM. Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. Clin Nutr. 2011 Jun;30(3):365-8.
3. McCray S, Walker S, Parrish CR. Much ado about refeeding. Pract Gastroenterol 2004;28:26-44.
4. Burger GC, Drummond J, Sandstead HR: Appendices to malnutrition and starvation in western Netherlands September 1944–July 1945 (part II) [internet]. The Hague General State Printing Office; 1948. Available from: http://apps.who.int/iris/bitstream/handle/10665/101051/WHA4_4_eng.pdf;jsessionid=0B41E6B899758A8FA62BEA1BAB03EDAA?sequence=1 [Accessed May 22, 2018].
5. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med. 1951 Jul;35(1):69-96.
6. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: Results of a systematic review. Nutrition. 2017 Mar;35:151-160.
7. van Zanten ARH. Nutritional support and refeeding syndrome in critical illness. Lancet Respir Med 2015 Dec;3(12):904-5.
8. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013 Jan 11;3(1):e002173.
9. Matthews KL, Capra SM, Palmer MA. Throw caution to the wind: is refeeding syndrome really a cause of death in acute care? Eur J Clin Nutr. 2018 Jan;72(1):93-98.
10. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clin Nutr. 2018 Oct;37(5):1609-1617.
11. Coşkun R, Gündoğan K, Baldane S, Güven M, Sungur M. Refeeding hypophosphatemia: a potentially fatal danger in the intensive care unit. Turk J Med Sci. 2014;44(3):369-74.
12. Fuentes E, Yeh DD, Quraishi SA, Johnson EA, Kaafarani H, Lee J, et al. Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive Care Unit. Nutr Clin Pract. 2017 Apr;32(2):252-257.
13. Vignaud M, Constantin JM, Ruivard M, Villemeyre-Plane M, Futier E, Bazin JE, et al; AZUREA group (AnorexieRea Study Group). Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study. Crit Care. 2010;14(5):R172.
14. Hernández-Aranda JC, Gallo-Chico B, Luna-Cruz ML, Rayón-González MI, Flores-Ramírez LA, Ramos Muñoz R, et al. Malnutrition and total parenteral nutrition: a cohort study to determine the incidence of refeeding syndrome. Rev Gastroenterol Mex. 1997 Oct-Dec;62(4):260-5.
15. Obeid OA, Hachem DH, Ayoub JJ. Refeeding and metabolic syndromes: two sides of the same coin. Nutr Diabetes. 2014 Jun 30;4(6):e120.
16. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al; Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015 Dec;3(12):943-52.
17. Nutrition support for adults: oral nutrition support, enteral tube feeding, and parenteral nutrition. Guidance and guidelines. NICE [Internet]. Nice.org.uk. 2018. Available from: https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#screening-for-malnutrition-and-the-risk-of-malnutrition-in-hospital-and-the-community [Accessed May 22, 2018].

18. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z; Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003 Jun;22(3):321-36.
19. Koekkoek KWAC, van Zanten ARH. Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding? Curr Opin Anaesthesiol. 2018 Apr;31(2):136-143.
20. Bousie E, van Blokland D, Lammers HJ, van Zanten ARH. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr. 2016 Dec;70(12):1443-1450.

CHAPTER 5

5

Macronutrient intake and outcomes of ICU patients with refeeding hypophosphatemia

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Abstract

Background

Normocaloric vs. calorie-restricted feeding in Intensive care unit (ICU) patients with refeeding hypophosphatemia (RH) is associated with increased mortality rates. Until now, only total energy provision has been studied. Data on individual macronutrients (proteins, lipids, and carbohydrates) and clinical outcomes are lacking. This study evaluates associations between macronutrient intake among RH patients during the first week of ICU admission and clinical outcomes.

Methods

A single-centre retrospective observational cohort study was conducted among prolonged mechanically ventilated RH ICU patients. The primary outcome was the association of separate macronutrient intakes during the first week of ICU admission with 6-month mortality, adjusted for relevant variables. Other parameters included ICU-, hospital- and 3-month mortality, mechanical ventilation duration and length of ICU and hospital stay. Macronutrient intakes were subsequently analyzed during day 1-3 and day 4-7 of ICU admission.

Results

In total, 178 RH patients were included. Six-month all-cause mortality was 29.8%. Higher protein intake during days 1-3 of ICU admission (>0.71 g/kg*day; HR 2.224, 95% CI 1.261-3.923, p=0.006), higher age (HR 1.040, 95% CI 1.015-1.066, p=0.002) and higher APACHE II scores on ICU admission (HR 1.086, 95% CI 1.034-1.140, p=0.001) were associated with increased 6-month mortality. No differences in other outcomes were observed.

Conclusion

High protein - not carbohydrate or lipid - intake during the first three days of ICU admission in patients with RH is associated with increased 6-month mortality, but not short-term outcomes. We hypothesize a time-dependent and dose-response relationship between protein intake and mortality in refeeding hypophosphatemia ICU patients, although additional (randomized controlled) studies are needed to confirm this hypothesis.

Introduction

The reintroduction of macronutrients (proteins, lipids, carbohydrates) after a period of fasting or starvation might induce refeeding syndrome (RFS) in patients at risk (1-7). RFS describes a spectrum of clinical symptoms resulting from biochemical abnormalities, typically consisting of fluid and electrolyte imbalances with refeeding hypophosphatemia (RH) playing a central role. Additionally, abnormalities in glucose metabolism and vitamin (thiamine) deficiencies are frequently seen (3-6,8-11). Clinical symptoms are diverse, and multiple organ systems may be involved. Neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications lead to multisystem organ failure and, ultimately, death if not adequately treated (1,3,8-10,12-14).

Standard treatment of RH consists of strict monitoring of the patient, correction of electrolyte disorders, suppletion of vitamins (particularly thiamine), and, if necessary, fluid correction and insulin therapy (1,5,6,10-13). There has been considerable debate about energy intake during this period; recommendations vary between a full energy strategy, restricted intake and immediate discontinuation of nutritional therapy (1,2,4,5,7,8,10,11,13,15,16). The European Society for Clinical Nutrition and Metabolism (ESPEN) and National Institute for Health and Care Excellence (NICE) guidelines recommend "start low and go slow", i.e., to gradually increase energy intake after a restricted-energy supply during the first 48 hours of feeding (17,18). Based on the recent observations by Doig *et al.*, a restriction of energy intake at 480 kcal/24 h for at least 48 hours is recommended (15). In a randomized, multicentre, single-blind controlled trial, Doig and co-workers found that normocaloric feeding in RH patients admitted to an Intensive care unit (ICU) was associated with higher 60- and 90-day mortality rates (p=0.002 and p=0.041 respectively) (15). Olthof *et al.* demonstrated a 6-month mortality reduction in RH patients who received hypocaloric feeding (<50% of calculated energy targets) in the first 72 hours after ICU admission compared with RH patients who received more than 50% of calculated targets (adjusted hazard ratio (HR) 0.39, 95% confidence interval (95% CI) 0.16–0.95, p=0.037) (1).

All current literature addresses the total energy provision but not specific macronutrients which are associated with higher mortality (19-22). Nevertheless, there is increasing evidence that macronutrient intake, especially adequate and time-dependent protein provision, is more important than cumulative energy intake in critical illness (21-28). Sufficient protein delivery is associated with improved survival (19,22,23,29-34). Critically ill patients are hypercatabolic and may require up to 2.2-3.5 grams of proteins per kilogram body weight per day to approach nitrogen balance (19). On the other hand, increased protein delivery in the first week of critical illness has been associated with enhanced muscle wasting (29,35). Recently, Koekkoek and colleagues conducted

a retrospective study to identify the optimum timing and dose of proteins in critically ill patients who are mechanically ventilated for at least seven days. Their results show that low protein intake (≤0.8 g/kg/day) in the first two days after ICU admission, intermediate (0.8-1.2 g/kg/day) during days 3-5 and subsequently high intake (≥1.2 g/kg/day) was associated with reduced 6-month mortality rates (24). It has been proposed that early feeding (and thus protein administration) may inhibit autophagy and harm the critically ill patient in the acute phase of illness (24,28,32,36-39). Whether this is true for patients with RH as well is not known. Moreover, until now, no studies have been published on the associations of the individual macronutrients with outcomes of critically ill patients with RH.

The current study aimed to evaluate a possible association between 6-month mortality and individual macronutrients (proteins, lipids, carbohydrates) administered in the first week of ICU admission in mechanically ventilated ICU patients diagnosed with RH, irrespective of energy intake. Secondary outcomes were ICU-, hospital- and 3-month mortality, duration of mechanical ventilation and ICU and hospital length of stay (LOS). We hypothesize that RH patients with lower protein intake during the early acute phase of ICU admission (days 1-3) have a survival benefit compared to RH patients with higher protein intake.

Materials and methods

Study design

A single-centre retrospective observational cohort study was conducted in critically ill mechanically ventilated patients admitted to the mixed medical-surgical ICU of Gelderse Vallei hospital (ZGV, The Netherlands). This current study is a follow-up to the initial case-control study by Olthof *et al.*, which studied the impact of energy intake during the first week of ICU admission in 124 critically ill mechanically ventilated patients with RH in the period 1-1-2011 until 31-12-2015 (hereafter called "cohort 1") (1). A new cohort of RH patients (hereafter called "cohort 2") who had been admitted to the ICU between 1-1-2016 and 31-12-2018 was added to this existing cohort. Before this, baseline characteristics and nutritional data of both cohorts were compared to identify statistically significant differences that would hamper pooling. If this were the case, both cohorts would not be pooled.

Study participants

Adult patients (aged ≥18 years) being invasively mechanically ventilated for ≥7 days and receiving enteral or parenteral nutritional (EN/PN) support were identified. Only patients who developed RH were eligible, defined as new hypophosphatemia

developed within 72 hours after initiation of (par)enteral nutrition. Patients without RH and/or receiving EN/PN prior to ICU admission were excluded. Hypophosphatemia was determined by a phosphate drop of >0.16 mmol/L from a previous normal reading to below 0.65 mmol/L (1,12,15,16). Patients were excluded when baseline phosphate levels on admission were low (<0.65 mmol/L) or if other causes of low serum phosphate were likely, such as renal replacement therapy, recent parathyroidectomy or treatment for hyperphosphatemia. Furthermore, patients were excluded when nutritional provision data or phosphate values were incomplete. Only the first admission was evaluated in case of ICU readmission within six months after ICU discharge. Based on our local ICU protocol, all patients received daily thiamine and electrolyte (potassium, magnesium, and phosphate) supplementation.

Data collection

Data collection from the patient data management system (PDMS) included patient characteristics (age, gender, anthropometry, comorbidities), admission type (medical, surgical or trauma), several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Nutrition Risk In Critically ill (NUTRIC), Charlson Comorbidity Index (CCI)), laboratory phosphate values, and lastly, duration of mechanical ventilation, ICU and hospital stay. Data extraction was performed using queries searching the ICU PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (NeoZis; MI Consultancy, Katwijk, The Netherlands).

Regarding nutritional intake, macronutrient data from the first seven days of ICU admission (including daily protein, carbohydrate, and lipid intake from (par)enteral nutrition and propofol, trisodium citrate and glucose infusions) were collected manually. Nutritional and non-nutritional macronutrient intakes were combined to calculate total energy, protein, carbohydrate and lipid loads in kilocalories (kcal) and grams (g) per kilogram (kg) actual bodyweight per day.

All parameters of interest were routinely collected during standard clinical care and therefore imposed no burden or risk to patients. The National Population Register was consulted for death records. Data verification was conducted manually.

Calculation of targets

To guide nutritional support, energy and protein targets were calculated using the Food and Agricultural Organization and World Health Organization (FAO/WHO/UNU) formulas, adapted for specific patient groups according to the local ICU protocol (see **Supplement 1**). Intake targets on the day of ICU admission (day 1) were adjusted for the actual time spent in the ICU this day. Days were defined as calendar days.

Day 1-3 was called the acute early phase of critical illness, and day 4-7 was the acute late phase (adapted according to the terminology of the ESPEN critical care guidelines) (17).

Nutrition in RH patients

All patients in our ICU received nutritional support and glucose control according to our local ICU protocol. During the first 3 days, energy and protein intake are gradually increased in steps of 25% to full target on day 4. However, when RH is detected nutritional support is reduced to 25% of calculated energy and protein requirements and gradually increased from day three onwards with 25% per day (to a full strategy on day 5). Of note, an electronic energy restriction protocol for RH was implemented in our ICU in September 2017. This resulted in an immediate adaptation of energy- and protein targets, activated when refeeding hypophosphatemia occurred.

Study endpoints

The primary outcome of this study was 6-month mortality and its association with individual macronutrients (proteins, lipids, carbohydrates) administered in the first week of ICU admission, adjusted for other variables relevant for this endpoint. Secondary outcomes included ICU-, in-hospital- and 3-month mortality, duration of mechanical ventilation and ICU and hospital LOS. Early (day 1-3 of ICU admission) and late (day 4-7) acute phase intake of the macronutrients were subsequently analyzed.

Subgroup analyses were performed based on achieving less or more than 50% of prescribed cumulative energy targets during days 1-3 of ICU admission. The outcomes of the low (<50% of calculated targets) versus the high (>50%) intake groups were compared.

Statistical analysis

Discrete variables were reported as proportions. Continuous data were expressed as means, including standard deviations (SD) or, in the case of non-parametric data, as medians with interquartile ranges (IQR).

In the case of non-linearity with the outcome parameter, macronutrient intakes in g/kg per day were dichotomized. Cut-off values were chosen based on the assessment of Kaplan Meier curves of individual macronutrient intakes concerning 6-month mortality. Curves were compared using the Log-rank test. The dichotomized individual macronutrients (in g/kg*day) and all relevant variables for 6-month mortality based on current literature were included successively in the univariable Cox regression analysis to assess the primary study endpoint. Secondary outcome parameters were assessed using Cox or linear regression models where appropriate. Variables with a p-value <0.10 or deemed clinically relevant were included in multivariable regression analyses.

These were: age, gender, BMI, APACHE II score on ICU admission and the intake of the separate macronutrients (proteins, carbohydrates and lipids). Multivariable Cox regression was conducted using the Forward Stepwise Wald and the Enter method. Morbidity outcomes were corrected for mortality as competing risk. The variance inflation factor (VIF) was used to detect multicollinearity. A VIF <2 was considered acceptable. All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA; 2016). Normality was assessed numerically and graphically (visual inspection of histograms and Q-Q plots). P-values <0.05 were considered statistically significant. P-values <0.10 were considered trends.

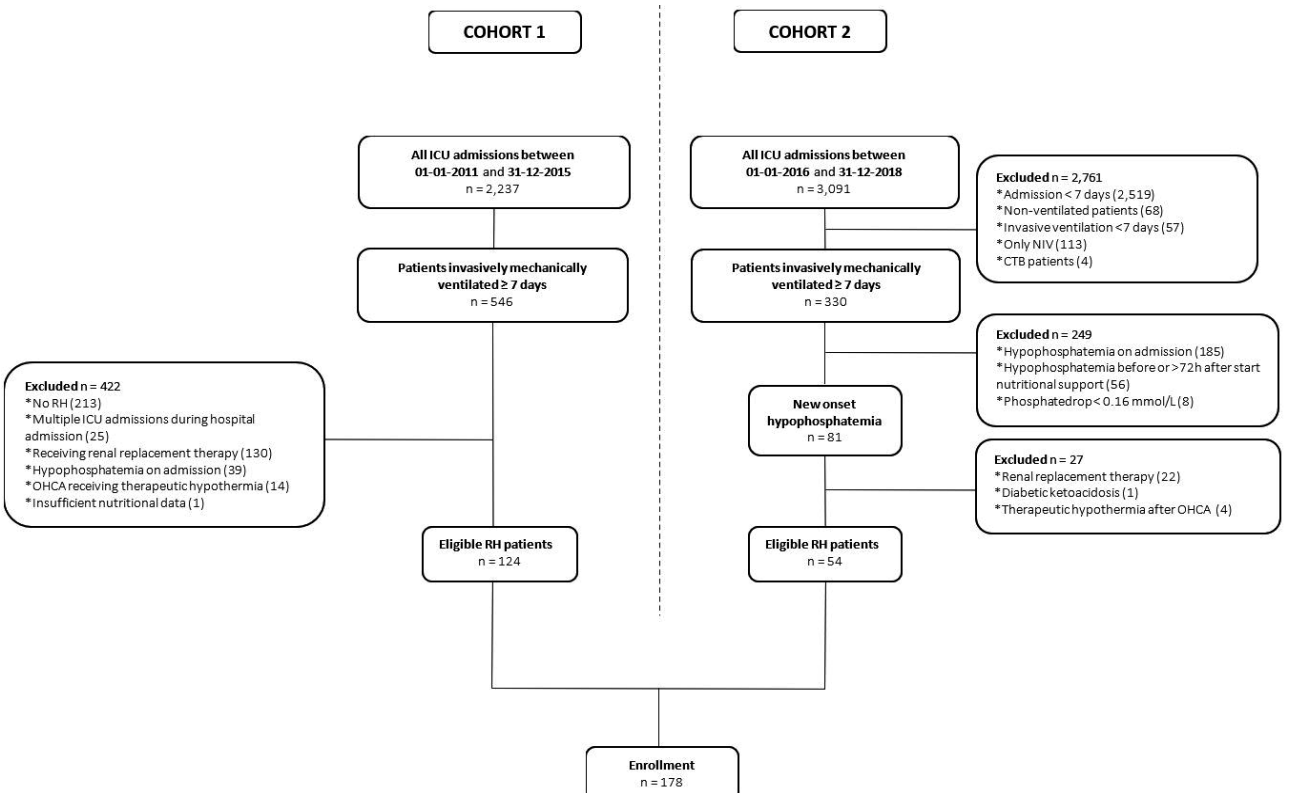
Ethical approval

The ethical approval committee of ZGV approved the study (study protocol number 1907-050). The retrospective study design and data anonymization provided a waiver concerning informed consent.

Results

During the study period, a total number of 3,091 patients were admitted to the ICU. Of these, 54 patients were eligible for inclusion (hereafter called "cohort 2") (see **Figure 1**). Data of this cohort was pooled with the existing Olthof cohort from our group (n=124, hereafter called "cohort 1") after a comparison of baseline characteristics, nutritional data and outcomes of both cohorts (see **Supplements 2-4**).

Figure 1. Study flowchart



CTB = chronic non-invasive mechanical ventilation at home; ICU = Intensive care unit; NIV = noninvasive ventilation; OHCA = out of hospital cardiac arrest; RH = refeeding hypophosphatemia;
Cohort 1: cohort 2011-2015 ("Olthof cohort"); Cohort 2: cohort 2016-2018 ("Boot cohort").

Pooling cohorts

Cohort 2 had higher mean SOFA scores on ICU admission (8.1 (SD 2.6) versus 6.6 (2.7), p=0.001), and lower serum phosphate levels (median 0.94 [IQR 0.84-1.19] versus 1.14 [0.95-1.37] mmol/L, p=0.002) compared to cohort 1. Moreover, higher serum glucose levels were seen in the first 24 hours after ICU admission in cohort 2 (median 10.2 [8.6-12.9] versus 7.5 [6.5-8.7] mmol/L, p<0.001), although a trend towards lower cumulative insulin doses at day 7 (p=0.085) was seen. Regarding nutritional intake, cohort 2 had significant lower protein (0.45 (SD 0.29) versus 0.64 (0.31) g/kg/day ideal body weight, p<0.001) and carbohydrate (4.8 (SD 2.5) versus 6.1 (2.9) kcal/kg/day, p=0.006) intake in the first three days of nutritional support after ICU admission. During days 4-7, this cohort 2 also had a significantly lower intake of all macronutrients (p<0.001), as shown in **Supplement 3**. In addition to this, a higher percentage of patients from cohort 2 received energy (and protein) restriction, defined as an intake of <50% of prescribed targets, during day 1-3 (energy restriction 48.1% versus 25.8% (p=0.003); protein restriction 72.2% versus 45.2% (p=0.001)). Of note, 15 (27.8%) patients from cohort 2 were included from September 2017 onwards, benefiting from an immediate adaptation of their energy- and protein targets by the electronic energy restriction protocol when RH occurred.

Moreover, the percentage of non-nutritional calories to total caloric load were significant higher in cohort 2 (3-day propofol infusions: median 12.2% [3.7-25.8] versus 2.5% [0.0-10.0], p<0.001; 3-day glucose infusions: 15.0% [6.2-27.5] versus 9.7% [1.0-17.4], p=0.004). Finally, a statistically significant difference in 3-month mortality was seen in the benefit of cohort 2 (16.7 versus 33.1%, p=0.025) (see **Supplement 4**). The baseline and nutritional characteristics of the pooled cohort are shown in **Tables 1 and 2**.

Table 1. Baseline characteristics

Gender (male)	*N (%)*	106 (59.6)
Age (years)	*median [IQR]*	68.0 [57-76]
Weight on admission (kg)	*median [IQR]*	78 [67-90]
Length on admission (cm)	*median [IQR]*	172 [166-178]
BMI on ICU admission (kg/m2)	*median [IQR]*	26.1 [23.1-29.3]
BMI <18.5	*N (%)*	8 (4.5)
Sepsis on ICU admission	*N (%)*	91 (51.1)
APACHE II score on ICU admission [n=172]	*mean (SD)*	20.9 (5.7)
SOFA score on ICU admission	*mean (SD)*	7.1 (2.8)
Charlson Comorbidity Index	*mean (SD)*	3.6 (2.2)
NUTRIC score	*mean (SD)*	4.5 (1.6)
Baseline laboratory values	*median [IQR]*	
Leukocytes (x109/L)		13.8 [9.5-18.6]
Creatinine (µmol/L)		88 [67-110.3]
CRP (mg/L) [n=174]		114.5 [31-219.8]
Bilirubin (mmol/L) [n=173]		9 [6-14]
Albumin (g/L) [n=175]		27 [21-33]
Highest glucose first 24h (mmol/L) [n=166]		8.1 [6.7-10.3]
Baseline electrolytes (mmol/L)	*median [IQR]*	
Sodium		139 [135-142]
Potassium		3.7 [3.3-4.1]
Magnesium [n=172]		0.69 [0.59-0.80]
Phosphate		1.10 [0.89-1.33]
Admission type	*N (%)*	
Medical		110 (61.8)
Elective surgery		32 (18.0)
Emergency surgery		36 (20.2)

N = number of patients; IQR = interquartile range; SD = standard deviation; BMI = body mass index; ; ICU = intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; NUTRIC = Nutrition Risk In the Critically Ill; CRP = C-reactive protein.

Table 2. Nutritional data

Days until RH diagnosis	*mean (SD)*	2.9 (1.0)
Time until start nutrition (hours)	*median [IQR]*	7.0 [3.3-16.6]
Macronutrients (non-)nutritional (kcal/kg*day)	*mean (SD)*	18.2 (4.8)
day 1-3 energy intake (kcal/kg*day)		11.8 (5.2)
proteins		2.3 (1.3)
lipids		3.8 (2.3)
carbohydrates		5.7 (2.8)
day 4-7 energy intake		22.9 (5.7)
proteins		5.1 (1.2)
lipids		7.1 (3.5)
carbohydrates		10.6 (3.8)

Table 2. Continued

Days until RH diagnosis	*mean (SD)*	2.9 (1.0)
Macronutrients (non-)nutritional (g/kg*day)	*mean (SD)*	
day 1-3		
proteins		0.58 (0.31)
lipids		0.42 (0.26)
carbohydrates		1.42 (0.71)
day 4-7		
proteins		1.29 (0.30)
lipids		0.79 (0.39)
carbohydrates		2.66 (0.96)
Energy targets (kcal/kg*day)	*mean (SD)*	
PS ventilation		25.7 (4.2)
PC ventilation		23.7 (3.9)
Protein targets	*mean (SD)*	
in kcal/kg*day		6.1 (0.4)
in g/kg*day		1.5 (0.1)
Energy and protein adequacy (%)	*mean (SD)*	
day 1-3 energy adequacy (PS)		57.8 (23.0)
day 1-3 energy adequacy (PC)		62.6 (25.0)
day 4-7 energy adequacy (PS)		90.0 (20.5)
day 4-7 energy adequacy (PC)		97.5 (22.2)
day 1-3 protein adequacy		47.4 (24.6)
day 4-7 protein adequacy		84.3 (19.3)
Non-nutritional to total caloric load (%)	*median [IQR]*	
day 1-3 glucose		10.2 [2.5-20.2]
day 4-7 glucose		1.6 [0.4-5.0]
day 1-3 citrate		0 [0]
day 4-7 citrate		0 [0]
day 1-3 propofol		4.3 [0.4-13.9]
day 4-7 propofol		1.4 [0.0-6.0]
Insulin administration (IU/day)	*median [IQR]*	
day 1-3 insulin dose		47.5 [28.0-79.0]
day 4-7 insulin dose		63.9 [38.8-105.2]
Energy intake <50% of target day 1-3 (PS)	*N (%)*	71 (39.9)
Energy intake <50% of target day 1-3 (PC)	*N (%)*	58 (32.6)
Energy intake <50% of target day 4-7 (PS)	*N (%)*	8 (4.5)
Energy intake <50% of target day 4-7 (PC)	*N (%)*	7 (3.9)
Protein intake <50% of target day 1-3	*N (%)*	95 (53.4)
Protein intake <50% of target day 4-7	*N (%)*	10 (5.6)

RH = refeeding hypophosphatemia; SD = standard deviation; IQR = interquartile range; PS = pressure support mechanical ventilation; PC = pressure control mechanical ventilation; IU = international units.

Study population and nutritional intake

Of all included RH patients (n=178), most patients were male (59.6%), overweight (median body mass index (BMI) 26.1 kg/m^2), non-surgical (61.8%), and had sepsis on ICU admission (51.1%). Nutritional support was initiated after a median time of 7.0 hours after ICU admission [IQR 3.3-16.6]. RH was diagnosed at a mean of 2.9 (SD 1.0) days.

Mean energy intake was 11.8 (SD 5.2) and 22.9 (5.7) kcal/kg*day during the acute early (day 1-3) and acute late (day 4-7) phases, respectively. Regarding protein intake, this was 2.3 (SD 1.3; 0.58 g/kg*day) and 5.1 (SD 1.2; 1.29 g/kg*day) kcal/kg*day, respectively. In the first 72 hours after the commencement of nutritional support, 58 patients (32.6%) received energy restriction, defined as an intake of less than 50% of the energy target. About seven patients (3.9%) had a restricted energy intake during days 4-7. An overview of the mean intake of (non-) nutritional macronutrients is depicted in **Table 2**.

At baseline, significant differences between the low (intake <50% of calculated energy targets of day 1-3) and high (>50%) intake groups were found for BMI (median 27.2 versus 25.3, p=0.027) and SOFA score on ICU admission (mean 7.7 (SD 2.9) versus 6.7 (2.6); p=0.023). Moreover, higher serum glucose values in the first 24 hours were seen in the low energy intake group (median 9.3 versus 7.8 mmol/L, p=0.003), whereas in the high intake group, more insulin was administered during the first 72 hours of ICU admission (median 155 versus 121 units, p=0.034). Regarding nutritional intake, a significant difference in time until the commencement of nutritional therapy was found: median 15.7 [IQR 6.5-27.6] hours in the low energy intake group versus 5.4 [2.9-11.7] hours in the high energy intake group (p<0.001). These groups' energy and protein targets were similar (p=0.154 and p=0.288, respectively).

Primary outcome: 6-month mortality

Overall, 6-month mortality was 29.8% (n=53). In univariable analyses, there was no statistically significant difference in 6-month mortality between subgroups with <50% and >50% of reached energy targets during the first three days of ICU admission (energy intake mean 6.6 (SD 2.2) versus 14.3 (SD 4.4) kcal/kg*day; energy adequacy 20.7 versus 34.2%), although a trend may be seen in benefit of the low intake group (p=0.065, see **Table 3**). Regarding subgroups with <50% and >50% of reached energy targets during days 4-7 after commencement of nutritional support, there was no significant difference (energy intake mean 20.3 (SD 6.2) versus 24.2 (SD 5.1) kcal/kg*day; energy adequacy 28.6 versus 29.8%, p = 0.943).

Table 3. Outcomes energy intake subgroups

		RH patients	Energy target reached		p-value[a)]
		(n=178)	<50% (n=58)	>50% (n=120)	
Days 1-3					
Mortality	*N (%)*				
ICU		26 (14.6)	7 (12.1)	19 (15.8)	0.505
Hospital		38 (21.3)	10 (17.2)	28 (23.3)	0.353
3 months		50 (28.1)	11 (19.0)	39 (32.5)	0.060
6 months		53 (29.8)	12 (20.7)	41 (34.2)	0.065
Length of stay (days), TDA	*median [IQR]*				
ICU [n=152]		14 [11-23]	13 [11-20]	15 [10-24]	0.928
Hospital [n=140]		26 [18-39]	25 [17-36]	27 [19-41]	0.821
Mechanical ventilation (days) [n=152]	*median [IQR]*	10 [8-14]	9 [8-13]	10 [8-16]	0.969
Days 4-7					
Mortality	*N (%)*				
ICU		26 (14.6)	2 (28.6)	24 (14.0)	0.286
Hospital		38 (21.3)	2 (28.6)	36 (21.1)	0.634
3 months		50 (28.1)	2 (28.6)	48 (27.0)	0.977
6 months		53 (29.8)	2 (28.6)	51 (29.8)	0.943
Length of stay (days), TDA	*median [IQR]*				
ICU [n=152]		14 [11-23]	11 [10-41]	14 [11-23]	0.440
Hospital [n=140]		26 [18-39]	21 [17-50]	26 [19-39]	0.255
Mechanical ventilation (days) [n=152]	*median [IQR]*	10 [8-14]	9 [7-31]	10 [8-14]	0.600

RH = refeeding hypophosphatemia; N = number of patients; IQR = interquartile range; ICU = intensive care unit; TDA = time to discharge alive;

< 50% energy target = less than 50 percent of energy targets reached during day 1-3 and 4-7 of ICU admission, respectively;

> 50% energy target = more than 50 percent of energy targets reached during day 1-3 and 4-7 of ICU admission, respectively;

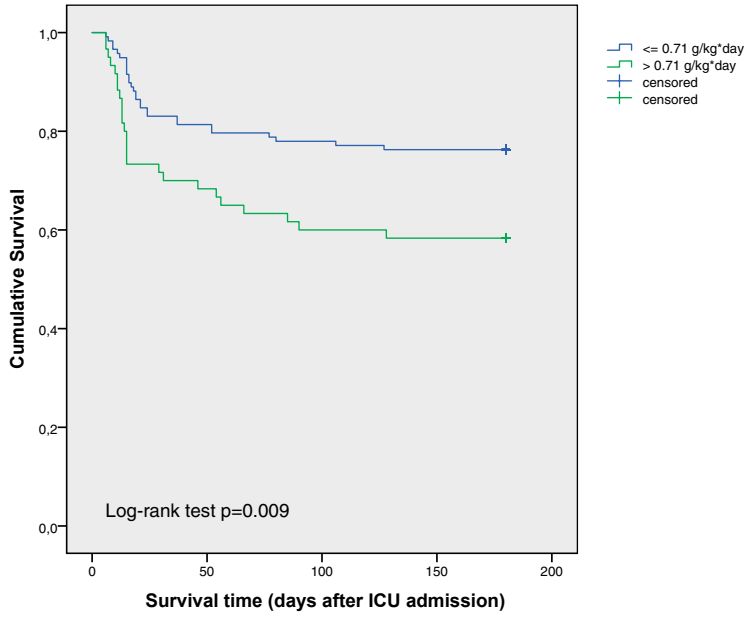
[a)] p-values were calculated using the chi-square or Mann-Whitney U test where appropriate.

The variables age, gender, BMI, APACHE II score and total energy intake during the first three days of ICU admission were considered relevant for univariable Cox regression for the association with 6-month mortality and individual macronutrient intake. However, total energy intake during days 1-3 and 4-7 was left out because matrix plots strongly correlated with the individual macronutrients. Because of non-linearity, all macronutrient variables were dichotomized based on the Kaplan Meier survival curves (see **Supplement 5**). Early (day 1-3 of ICU admission) and late (day 4-7) acute phase intake of the macronutrients were subsequently analyzed.

Early acute phase (day 1-3)

Univariable Cox regression analysis showed a significant survival benefit of lower age (HR 1.043, 95% CI 1.018-1.069, p=0.001), lower APACHE II score (HR 1.069, 95% CI 1.023-1.117, p=0.003), lower protein intake (≤0.71 gr/kg*day during days 1-3; HR 2.201, 95% CI 1.178-3.466, p=0.011, **Figure 2**) and lower carbohydrate intake (≤1.02 g/kg*day during days 1-3; HR 2.498; 95% CI 1.255-4.973, p=0.009). Lipid intake was not statistically significant (p=0.340). In the multivariable model, age (HR 1.040, 95% CI 1.015-1.066, p=0.002), APACHE II score on ICU admission (HR 1.086, 95% CI 1.034-1.140, p=0.001) and protein intake during days 1-3 (HR 2.224, 95% CI 1.261-3.923, p=0.006) were associated with the primary endpoint of 6-month mortality, as shown in **Table 4**. The VIF was <2 for the variables in this final model.

Figure 2. Kaplan Meier curve for 6-month survival comparing a protein intake of ≤0.71 and >0.71 g/kg*day during day 1-3 of ICU admission



ICU = Intensive care unit.

Table 4. Univariable and multivariable COX regressions for the association of primary endpoint 6-month mortality and macronutrient intake

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Days 1-3				
Age (years)	1.043 (1.018-1.069)	0.001*	1.040 (1.015-1.066)	0.002*
Gender (male)	1.386 (0.785-2.448)	0.260	1.557 (0.858-2.827)	0.145
BMI (kg/m^2)	0.946 (0.893-1.001)	0.055	0.963 (0.903-1.027)	0.254
APACHE II score on ICU admission	1.069 (1.023-1.117)	0.003*	1.086 (1.034-1.140)	0.001*
Protein intake (≤ 0.71 g/kg*day)	2.201 (1.178-3.466)	0.011*	2.224 (1.261-3.923)	0.006*
Lipid intake (≤ 0.51 g/kg*day)	1.311 (0.752-2.284)	0.340	0.998 (0.487-2.046)	0.996
Carbohydrate intake (≤ 1.02 g/kg*day)	2.498 (1.255-4.973)	0.009*	1.911 (0.838-4.359)	0.124
Days 4-7				
Age (years)	1.043 (1.018-1.069)	0.001*	1.042 (1.016-1.068)	0.001*
Gender (male)	1.386 (0.785-2.448)	0.260	1.445 (0.792-2.637)	0.230
BMI (kg/m^2)	0.946 (0.893-1.001)	0.055	0.962 (0.898-1.029)	0.257
APACHE II score on ICU admission	1.069 (1.023-1.117)	0.003*	1.074 (1.024-1.126)	0.003*
Protein intake (≤ 1.36 g/kg*day)	0.886 (0.517-1.520)	0.661	0.814 (0.429-1.541)	0.527
Lipid intake (≤ 0.77 g/kg*day)	0.970 (0.566-1.663)	0.912	1.155 (0.633-2.111)	0.638
Carbohydrate intake (≤ 2.58 g/kg*day)	1.485 (0.860-2.565)	0.156	1.460 (0.717-2.975)	0.297

95% CI = 95% confidence interval; HR = hazard ratio; BMI = body mass index; APACHE II = Acute Physiology And Chronic Health Evaluation II; ICU = intensive care unit;
**p-value <0.05.*

Late acute phase (day 4-7)

Univariable and multivariable COX regression analyses showed a significant survival benefit of lower age and APACHE II scores (see **Table 4**). No statistically significant association between macronutrient intake during the first week of ICU admission and 6-month mortality was demonstrated in univariable and multivariable analyses.

Secondary outcomes

An overview of ICU-, in-hospital- and 3-month mortality, duration of mechanical ventilation, and ICU and hospital LOS for both low and high energy intake groups is summarized in **Table 3**. There were no statistically significant differences between both subgroups in these secondary outcomes, although a trend in 3-month mortality was seen ($p<0.10$), favouring the group which received energy restriction during days 1-3.

Regarding macronutrient intake and secondary outcomes, no statistically significant associations were observed (**Supplements 6**).

Discussion

Primary study endpoint: 6-month mortality

In this study, we found a significant association between 6-month mortality and protein intake of RH patients during days 1-3 of ICU admission in multivariable models, favouring the low intake group (≤0.71 g/kg*day; HR 2.224, 95% CI 1.261-3.923, p=0.006). To date, no studies have been published investigating the association between macronutrient (more specific proteins) intake of RH patients and clinical outcomes (amongst others, 6-month mortality). Moreover, literature about protein intake and clinical outcomes in critically ill in general (RH and non-RH patients) is scarce and shows heterogenous methodology (study populations, measurement of nutritional intake, endpoints) and conflicting results, making a thorough comparison difficult. Our findings are consistent with Koekkoek *et al.* who demonstrated a time-dependent effect of protein intake in a non-RH mechanical ventilated ICU population (n=455), with the lowest 6-month mortality in the patient group with low protein provision (i.e. <0.8 g/kg*day; HR for >0.8 g/kg*day: 1.231, 95% CI, 1.040-1.457, p=0.016) during the early acute (day 1-3), and intermediate protein administration (i.e. 0.8-1.2 g/kg*day; HR 0.716, 95% CI 0.558-0.917, p=0.008) during the late acute phase (day 4-7) (24). Of note, this study did not distinguish between RH and non-RH patients, limiting the comparison with our results. No other studies evaluating macronutrient intake and 6-month mortality in general ICU populations were found.

Secondary outcomes

Regarding our secondary study aims (ICU-, in-hospital- and 3-month mortality, duration of mechanical ventilation, and ICU and hospital LOS), no statistically significant associations between macronutrient intake in the first week of ICU admission and clinical outcomes were demonstrated in multivariable analyses. No studies were found in current literature investigating these outcomes and macronutrient intake in RH patients.

Until now, explanatory mechanisms are lacking for the time-dependent and dose-response association of protein intake and clinical outcomes in critically ill patients. Patients are highly catabolic during the acute phase of critical illness, resulting in a high protein turnover to provide energy and enhanced synthesis of acute-phase response proteins, whereas skeletal muscle protein synthesis may be decreased (20,24,34). However, in later phases of critical illness, amino acids are essential for protein synthesis and are involved in immune function to supporting recovery (21,24). Additional protein supplementation in the early acute phase may inhibit or result in dysfunctional autophagy, leading to increased cell damage and loss of organ function (28,37). Another explanation may be that more protein provision during the early phase may increase

the oxidative burden (28). Finally, early mitochondrial dysfunction leads to energy deficits, inducing proteostatic effects. In this phase, protein administration may lead to enhanced muscle wasting and hepatic protein breakdown in the context of elevated glucagon levels (34,40).

Strikingly, we found no association with protein intake and short-term outcomes, such as ICU or 3-month mortality. These findings are in contrast with Koekkoek and colleagues, who demonstrated an association between time-dependent protein intake and ICU and hospital mortality, favouring the group with restricted protein intake during the first 3 days (24). It remains unclear why higher protein intake in the early acute phase results is associated with an increased long-term mortality (i.e. 6-months), but not with short-term outcomes in our study. We speculate that this might be partly due to the higher hospital and ICU readmission rates observed in the higher protein group compared to the patients who receive less proteins during the first 72h of ICU admission (41.7 versus 42.4% and 6.7 versus 5.1%), suggesting that these patients may survive their ICU and hospital admission, but have worse recovery and are prone to be readmitted with poor outcomes. Another possible and more plausible explanation is that there were additional confounding factors which were not accounted for (residual confounding).

Restricted energy intake

In univariable analysis, we did not find a statistically significant difference in 6-month mortality between RH subgroups with <50% and >50% of reached energy targets during days 1-3 and 4-7 of ICU admission (p=0.065 and p=0.943, respectively); only a trend was seen in the benefit of the low energy intake group at days 1-3 (p<0.10). This observation is in contrast with the findings of Doig *et al.*, who found a significant increased overall survival time and reduced mortality at day 60 follow-up (35 (21%) versus 15 (9%) for the group receiving energy restriction during treatment for RH (15). Of note, in earlier analyses of the first part of our cohort (cohort 1, n=124) by Olthof *et al.*, a significant increase in overall survival time for the hypocaloric group in univariable and multivariable COX regressions (HR 0.39, 95% CI 0.16-0.95, p=0.037) was demonstrated as well (1). This striking difference may be explained by the fact that the additional cohort (cohort 2, n=54), of whom more patients received energy restriction (48.1% versus 25.8%, p=0.003), had higher SOFA scores on ICU admission (8.1 (SD 2.6) versus 6.6 (SD 2.7), p=0.001), higher glucose values in the first 24 hours (median 10.2 [8.6-12.9] versus 7.5 [6.5-8.7], p<0.001) and lower phosphate laboratory values (0.94 [0.84-1.19] versus 1.14 [0.95-1.37], p=0.002), suggesting that this second cohort was more severely ill. Moreover, as already noticed, the entire cohort 2 had significantly lower protein intake in the first three days of nutritional support after ICU admission compared to cohort 1 (0.45 versus 0.64 g/kg*day ideal body weight, p<0.001), whether receiving energy restriction or not. These observations might have blunted the survival benefit in

hypocaloric-fed patients. Similar findings were reported in a randomized controlled trial by Arabi *et al.* (41). They studied permissive underfeeding (defined as 40-60% of energy targets) versus standard feeding (defined as 70-100% of energy targets) in 894 critically ill patients. No significant association with mortality up to 6 months was demonstrated. (41). However, additional protein supplements were administered in the permissive underfeeding group, which might have influenced their results. Although speculative, this may suggest that the protein supplementation in the permissive underfeeding group has impacted the effect of energy restriction on the outcome.

The significant difference in energy restriction observed between both cohorts in our study may be explained by the fact that in September 2017, an electronic energy restriction protocol for RH was implemented in our ICU. As mentioned in the methods section, this resulted in an immediate adaptation of energy- and protein targets which was activated when RH occurred.

Strengths

The extensive data set of (non-) nutritional intake during the (at least) first seven days of ICU admission of 178 critically ill patients with RH and a long follow-up period of 6 months are considered strengths of this study. Nutritional support was started early after ICU admission (median 7.0 hours) compared to current literature (e.g., Doig *et al.* reported a mean of 1.4 days; Koekkoek *et al.* median 5.6 hours (15,24).

Limitations

First of all, the retrospective, observational design of our study may have introduced bias and residual confounding. Moreover, there is a significant risk of selection bias due to the exclusion of patients with early mortality and early alive ICU discharge (exclusion criterium: mechanical ventilation <7 days). Thirdly, the long study period (2011-2018), including a defined change in nutrition delivery through adoption of the electronic energy restriction protocol, may have contributed to the heterogeneous study population and additional bias. Fourthly, we might have introduced bias by defining the cut-off values; the outcome may depend on how well the cut-off values have been chosen (22). Fifthly, the strong association between caloric and macronutrient intake carries the risk of confounding in multivariable analyses (especially protein and carbohydrate intake), although we tried to correct for this. Furthermore, it is a single-centre study, and we only included critically ill patients with RH who were mechanically ventilated for at least seven days limiting the external validity. Also, we did not correct data for pre-ICU nutrition status and adherence to micronutrient supplementation in the ICU (34,43). Finally, energy targets were based on a static formula (FAO/WHO/UNU), not accounting for individual needs (as measured with indirect calorimetry).

Further research

Additional (randomized controlled) studies are needed to confirm the hypothesis of a potential survival benefit in patients with low protein intake during days 1-3 of ICU admission, especially in patients with RH. The underlying mechanisms are still unclear. Future studies could include pre-ICU nutrition status, body composition and biomarkers of optimal protein intake, such as nitrogen balance, physical function tests, and clinical outcomes, as was previously suggested (20).

Moreover, indirect calorimetry should guide targeting the individual energy needs of patients after the initial ICU phase (around day four after ICU admission) as progressive energy increase during the first days of ICU stay is recommended (17,42).

Conclusion

Associations between 6-month mortality and protein intake during the first three days of ICU admission in critically ill patients with refeeding hypophosphatemia were found. All-cause six-month mortality was significantly lower in the low protein intake group (≤0.71 g/kg*day), but ICU, hospital, 3-month mortality and other secondary outcomes were not. No association with carbohydrate intake was demonstrated. We suggest a time-dependent association between early protein intake and 6-months mortality among refeeding hypophosphatemia patients, although additional studies are warranted to confirm this hypothesis. Our findings may implicate that when refeeding hypophosphatemia in critical illness is encountered, and thus total caloric restriction is warranted for some days, during this phase, no protein supplementation should be provided.

References

1. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clin Nutr. 2018 Oct;37(5):1609-1617.
2. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013 Jan 11;3(1):e002173.
3. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition. 2010 Feb;26(2):156-67.
4. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008 Jun 28;336(7659):1495-8.
5. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. Nutr Clin Pract. 2005 Dec;20(6):625-33.
6. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001 Jul-Aug;17(7-8):632-7.
7. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg. 1996 Oct;131(10):1043-7.
8. Fuentes E, Yeh DD, Quraishi SA, Johnson EA, Kaafarani H, Lee J, et al. Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive care unit. Nutr Clin Pract. 2017 Apr;32(2):252-257.
9. Obeid OA, Hachem DH, Ayoub JJ. Refeeding and metabolic syndromes: two sides of the same coin. Nutr Diabetes. 2014 Jun 30;4(6):e120.
10. Fernández López MT, López Otero MJ, Alvarez Vázquez P, Arias Delgado J, Varela Correa JJ. Refeeding syndrome. Farm Hosp. 2009 Jul-Aug;33(4):183-93.
11. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr. 1990 Jan-Feb;14(1):90-7.
12. Boot R, Koekkoek KWAC, van Zanten ARH. Refeeding syndrome: relevance for the critically ill patient. Curr Opin Crit Care. 2018 Aug;24(4):235-240.
13. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008 Jun;62(6):687-94.
14. Bugg NC, Jones JA. Hypophosphataemia. Pathophysiology, effects and management on the intensive care unit. Anaesthesia. 1998 Sep;53(9):895-902.
15. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al; Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015 Dec;3(12):943-52.
16. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: Results of a systematic review. Nutrition. 2017 Mar;35:151-160.
17. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019 Feb;38(1):48-79.
18. Nutrition support for adults: oral nutrition support, enteral tube feeding, and parenteral nutrition. Guidance and guidelines. NICE [Internet]. Nice.org.uk. 2022 [cited 22 January 2022]. Available from: https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#screening-for-malnutrition-and-the-risk-of-malnutrition-in-hospital-and-the-community

19. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study. JPEN J Parenter Enteral Nutr. 2016 Jan;40(1):45-51.
20. Preiser JC, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015 Jan 29;19(1):35.
21. Hoffer LJ, Bistrian BR. What is the best nutritional support for critically ill patients? Hepatobiliary Surg Nutr. 2014 Aug;3(4):172-4.
22. Weijs PJ, Wischmeyer PE. Optimizing energy and protein balance in the ICU. Curr Opin Clin Nutr Metab Care. 2013 Mar;16(2):194-201.
23. Singer P, Hiesmayr M, Biolo G, Felbinger TW, Berger MM, Goeters C, et al. Pragmatic approach to nutrition in the ICU: expert opinion regarding which calorie protein target. Clin Nutr. 2014 Apr;33(2):246-51.
24. Koekkoek WACK, van Setten CHC, Olthof LE, Kars JCNH, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study. Clin Nutr. 2019 Apr;38(2):883-890.
25. Koekkoek KWAC, van Zanten ARH. Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding? Curr Opin Anaesthesiol. 2018 Apr;31(2):136-143.
26. Hoffer LJ. High-Protein Hypocaloric Nutrition for Non-Obese Critically Ill Patients. Nutr Clin Pract. 2018 Jun;33(3):325-332.
27. Van Zanten ARH Should We Increase Protein Delivery During Critical Illness? JPEN J Parenter Enteral Nutr. 2016 Aug;40(6):756-62.
28. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med. 2013 Feb 1;187(3):247-55.
29. Lambell KJ, Tatucu-Babet OA, Chapple LA, Gantner D, Ridley EJ. Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care. 2020 Feb 4;24(1):35.
30. Song JH, Lee HS, Kim SY, Kim EY, Jung JY, Kang YA, et al. The influence of protein provision in the early phase of intensive care on clinical outcomes for critically ill patients on mechanical ventilation. Asia Pac J Clin Nutr. 2017 Mar;26(2):234-240.
31. Weijs PJ, McClave SA. The need to differentiate fear for energy overfeeding from future benefits of protein feeding: so much to gain! Curr Opin Clin Nutr Metab Care. 2016 Mar;19(2):116-9.
32. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014 Dec 14;18(6):701.
33. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012 Aug;31(4):462-8.
34. Tsai JR, Chang WT, Sheu CC, Wu YJ, Sheu YH, Liu PL, et al. Inadequate energy delivery during early critical illness correlates with increased risk of mortality in patients who survive at least seven days: a retrospective study. Clin Nutr. 2011 Apr;30(2):209-14.
35. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013 Oct 16;310(15):1591-600.
36. McClave SA, Weijs PJ. Preservation of autophagy should not direct nutritional therapy. Curr Opin Clin Nutr Metab Care. 2015 Mar;18(2):155-61.

37. Derde S, Vanhorebeek I, Güiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology. 2012 May;153(5):2267-76.
38. Schetz M, Casaer MP, Van den Berghe G. Does artificial nutrition improve outcome of critical illness? Crit Care. 2013 Feb 1;17(1):302.
39. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Güiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. 2011 Apr;96(4):E633-45.
40. Thiessen SE, Derde S, Derese I, Dufour T, Vega CA, Langouche L, et al. Role of Glucagon in Catabolism and Muscle Wasting of Critical Illness and Modulation by Nutrition. Am J Respir Crit Care Med. 2017 Nov 1;196(9):1131-1143.
41. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med. 2015 Jun 18;372(25):2398-408.
42. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care. 2019 Nov 21;23(1):368.

Supplementary Material

Supplement 1. Target calculations (energy / protein)

A) Energy targets

Resting energy expenditure

Male	
18-30y	15.4 x weight - 27 x length + 717
30-60y	11.3 x weight - 16 x length + 901
>60y	8.8 x weight + 1128 x length - 1071

Female	
18-30y	13.3 x weight + 334 x length + 35
30-60y	8.7 x weight - 25 x length + 865
>60y	9.2 x weight + 637 x length - 302

Adaptation to ICU patient

Pressure control ventilation	
BMI ≤ 27	REE + 20%
BMI 27-30	REE + 20% (weight corrected to BMI 27)
BMI ≥ 30	60-70% of REE + 20% (weight corrected to BMI 27)

Pressure support ventilation	
BMI ≤ 27	REE + 30%
BMI 27-30	REE + 30% (weight corrected to BMI 27)
BMI ≥ 30	60-70% of REE + 30% (weight corrected to BMI 27)

B) Protein targets

BMI ≤ 27	1.5 g/kg of actual body weight
BMI 27-30	1.5 g/kg, weight corrected to BMI 27
BMI 30-40	2.0 g/kg ideal body weight (male BMI 22.5; female BMI 21)
BMI ≥ 40	2.5 g/kg ideal body weight (male BMI 22.5; female BMI 21)

y = years; weight in kilograms; length in meters;
ICU = Intensive care unit; BMI = Body mass index; REE = resting energy expenditure.

Supplement 2. Baseline characteristics cohort 1 and 2

		All RH patients	Cohort 1	Cohort 2	p-value[a)]
		(n=178)	(n=124)	(n=54)	
Gender (male)	*N (%)*	106 (59.6)	74 (59.7)	32 (59.3)	0.958
Age (years)	*median [IQR]*	68 [57-76]	69 [58-76]	67 [51-76]	0.369
BMI on ICU admission (kg/m^2)	*median [IQR]*	26.1 [23.2-29.3]	25.7 [22.7-29.3]	27.0 [23.4-29.3]	0.253
BMI <18.5	*N (%)*	8 (4.5)	8 (6.5)	0 (0)	0.056
Charlson Comorbidity Index	*median [IQR]*	3 [2-5]	4 [2-5]	3 [1-5]	0.286
APACHE II score on ICU admission	*mean (SD)*	20.9 (5.7) (n=172)	21.3 (5.8) (n=118)	20 (5.6)	0.175
SOFA score on ICU admission	*mean (SD)*	7.1 (2.7)	6.6 (2.7)	8.1 (2.6)	0.001*
NUTRIC score on ICU admission	*mean (SD)*	4.5 (1.6)	4.5 (1.6)	4.5 (1.7)	0.920
Sepsis on ICU admission (yes)	*N (%)*	91 (51.1)	66 (53.2)	25 (46.3)	0.395
Baseline laboratory values	*median [IQR]*				
Highest glucose first 24h (mmol/L)		8.9 [6.7-10.3] (n=166)	7.5 [6.5-8.7] (n=112)	10.2 [8.6-12.9]	<0.001*
CRP (mg/L)		114.5 [31.0-219.8] (n=174)	117.0 [20.5-229.5] (n=120)	113.0 [48.0-191.5]	0.912
Leukocytes (x109/L)		13.8 [9.5-18.6]	14.1 [9.8-19.0]	12.2 [9.1-17.6]	0.194
Creatinine (µmol/L)		88.0 [67.0-110.3]	86.0 [66.3-110.5]	91.0 [68.0-110.3]	0.725
Bilirubin (mmol/L)		9 [6-14] (n=173)	9 [6-14] (n=119)	8 [6-19]	0.854
Albumin (g/L)		27 [21-33] (n=175)	28 [22-34] (n=122)	27 [21-31] (n=53)	0.181
Baseline electrolytes (mmol/L)	*median [IQR]*				
Phosphate		1.10 [0.89-1.33]	1.14 [0.95-1.37]	0.94 [0.84-1.19]	0.002*
Magnesium		0.69 [0.59-0.80] (n=172)	0.69 [0.58-0.80] (n=120)	0.69 [0.61-0.82] (n=52)	0.749
Sodium		139 [135-142]	139 [136-142]	140 [135-142]	0.683
Potassium		3.7 [3.3-4.1]	3.7 [3.2-4.1]	3.9 [3.4-4.4]	0.013*
Admission type (surgical)	*N (%)*	68 (38.2)	49 (39.5)	19 (35.2)	0.585
Need for tracheostomy (yes)	*N (%)*	35 (19.7)	22 (17.7)	13 (24.1)	0.328
Need for CRRT (yes)	*N (%)*	0 (0)	0 (0)	0 (0)	NA

Cohort 1: cohort 2011-2015 ("Olthof cohort"); Cohort 2: cohort 2016-2018 ("Boot cohort");
RH = refeeding hypophosphatemia; N = number of patients; IQR = interquartile range; SD = standard deviation; BMI = Body mass index; ICU = Intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; NUTRIC = Nutrition Risk In the Critically Ill; CRP = C-reactive protein; CRRT = Continuous Renal Replacement Therapy; NA = not applicable;
*a) p-values were calculated using the chi-square test, two sample t-test or Mann-Whitney U test where appropriate; * $p < 0.05$.*

Supplement 3. Nutritional data cohort 1 and 2

		All RH patients	Cohort 1	Cohort 2	p-value[a)]
		(n=178)	(n=124)	(n=54)	
Time until start nutrition (hours)	*median [IQR]*	7.0 [3.3-16.6]	6.4 [2.9-15.0]	9.6 [3.7-19.9]	0.117
Macronutrients (non-)nutritional (kcal/kg*day)	*mean (SD)*				
day 1-3 energy intake (kcal/kg*day)		11.8 (5.2)	12.6 (5.3)	10.1 (4.6)	0.004*
proteins		2.3 (1.3)	2.5 (1.2)	1.8 (1.1)	<0.001*
lipids		3.8 (2.3)	3.9 (2.4)	3.5 (2.1)	0.277
carbohydrates		5.7 (2.8)	6.1 (2.9)	4.8 (2.5)	0.006*
day 4-7 energy intake		22.9 (5.7)	24.1 (5.4)	20.2 (5.7)	<0.001*
proteins		5.1 (1.2)	5.4 (1.0)	4.6 (1.3)	<0.001*
lipids		7.1 (3.5)	7.5 (3.6)	6.3 (3.0)	0.036*
carbohydrates		10.6 (3.8)	11.2 (4.0)	9.3 (3.1)	0.003*
Macronutrients (non-)nutritional (g/kg*day)	*mean (SD)*				
day 1-3					
proteins		0.58 (0.31)	0.64 (0.31)	0.45 (0.29)	<0.001*
lipids		0.42 (0.26)	0.44 (0.27)	0.39 (0.23)	0.277
carbohydrates		1.42 (0.71)	1.52 (0.73)	1.20 (0.61)	0.006*
day 4-7					
proteins		1.29 (0.30)	1.34 (0.26)	1.15 (0.33)	<0.001*
lipids		0.79 (0.39)	0.83 (0.40)	0.70 (0.34)	0.036*
carbohydrates		2.66 (0.96)	2.80 (1.00)	2.33 (0.78)	0.003*
Energy targets (kcal/kg*day)	*mean (SD)*	23.7 (3.9)	23.7 (4.0)	23.7 (3.6)	0.995
Protein targets	*mean (SD)*				
in kcal/kg*day		6.1 (0.4)	6.1 (0.5)	6.1 (0.2)	0.314
in g/kg*day		1.5 (0.1)	1.5 (0.1)	1.5 (0.04)	0.314
Energy and protein adequacy (%)	*mean (SD)*				
day 1-3 energy adequacy (PS)		57.8 (23.0)	61.8 (23.8)	48.5 (18.3)	<0.001*
day 1-3 energy adequacy (PC)		62.6 (25.0)	67.0 (25.8)	52.5 (19.8)	<0.001*
day 4-7 energy adequacy (PS)		90.0 (20.5)	94.4 (17.8)	79.9 (22.7)	<0.001*
day 4-7 energy adequacy (PC)		97.5 (22.2)	102.3 (19.3)	86.5 (24.6)	<0.001*
day 1-3 protein adequacy		47.4 (24.6)	52.3 (24.2)	36.1 (21.9)	<0.001*
day 4-7 protein adequacy		84.3 (19.3)	88.0 (16.9)	75.9 (21.8)	<0.001*
Non-nutritional to total caloric load (%)	*median [IQR]*				
day 1-3 glucose		10.2 [2.5-20.2]	9.7 [1.0-17.4]	15.0 [6.2-27.5]	0.004*
day 4-7 glucose		1.6 [0.4-5.0]	1.6 [0.6-4.6]	1.4 [0.2-5.7]	0.914
day 1-3 citrate		0 [0]	NA	NA	NA
day 4-7 citrate		0 [0]	NA	NA	NA
day 1-3 propofol		4.3 [0.4-13.9]	2.5 [0.0-10.0]	12.2 [3.7-25.8]	<0.001*
day 4-7 propofol		1.4 [0.0-6.0]	0.6 [0.0-4.0]	3.7 [0.0-9.5]	0.006

Supplement 3. Continued

		All RH patients (n=178)	Cohort 1 (n=124)	Cohort 2 (n=54)	p-value[a)]
Insulin administration (IU/day)	*median [IQR]*				
day 1-3 insulindose		47.5 [28.0-79.0]	48.6 [29.4-82.4]	37.3 [22.5-76.1]	0.209
day 4-7 insulindose		63.9 [38.8-105.2]	64.8 [43.0-108.5]	59.4 [25.3-85.1]	0.111
Energy intake <50% of target day 1-3 (PS)	*N (%)*	71 (39.9)	42 (33.9)	29 (53.7)	0.013*
Energy intake <50% of target day 1-3 (PC)	*N (%)*	58 (32.6)	32 (25.8)	26 (48.1)	0.003*
Energy intake <50% of target day 4-7 (PS)	*N (%)*	8 (4.5)	3 (2.4)	5 (9.3)	0.056
Energy intake <50% of target day 4-7 (PC)	*N (%)*	7 (3.9)	3 (2.4)	4 (7.4)	0.201
Protein intake <50% of target day 1-3	*N (%)*	95 (53.4)	56 (45.2)	39 (72.2)	0.001*
Protein intake <50% of target day 4-7	*N (%)*	10 (5.6)	4 (3.2)	6 (11.1)	0.069

Cohort 1: cohort 2011-2015 ("Olthof cohort"); Cohort 2: cohort 2016-2018 ("Boot cohort");
RH = refeeding hypophosphatemia; IQR = interquartile range; SD = standard deviation; N = number of patients; PS = pressure support ventilation; PC = pressure control ventilation; NA = not applicable; IU = international units;
a) p-values were calculated using chi-square test, two sample t-test or Mann-Whitney U test where appropriate;
** p < 0.05.*

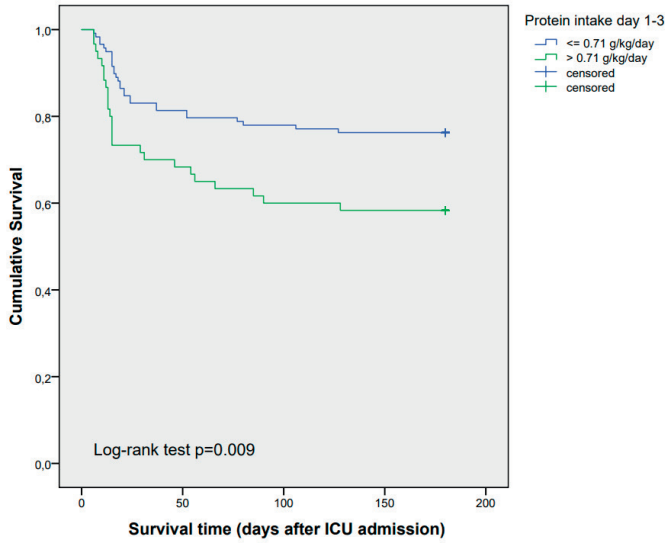
Supplement 4. Outcomes of cohort 1 and 2

		All RH patients (n=178)	Cohort 1 (n=124)	Cohort 2 (n=54)	p-value[a)]
Mortality	*N (%)*				
ICU		26 (14.6)	21 (16.9)	5 (9.3)	0.183
Hospital		38 (21.3)	30 (24.2)	8 (14.8)	0.160
3 months		50 (28.1)	41 (33.1)	9 (16.7)	0.025*
6 months		53 (29.8)	42 (33.9)	11 (20.4)	0.070
Length of stay (days), TDA	*median [IQR]*				
ICU [n=152]		14 [11-23]	15 [11-22]	13 [10-26]	0.505
Hospital [n=140]		26 [18-39]	28 [19-36]	24 [18-43]	0.929
Mechanical ventilation (days), [n=152]	*median [IQR]*	10 [8-14]	10 [8-14]	11 [8-15]	0.698

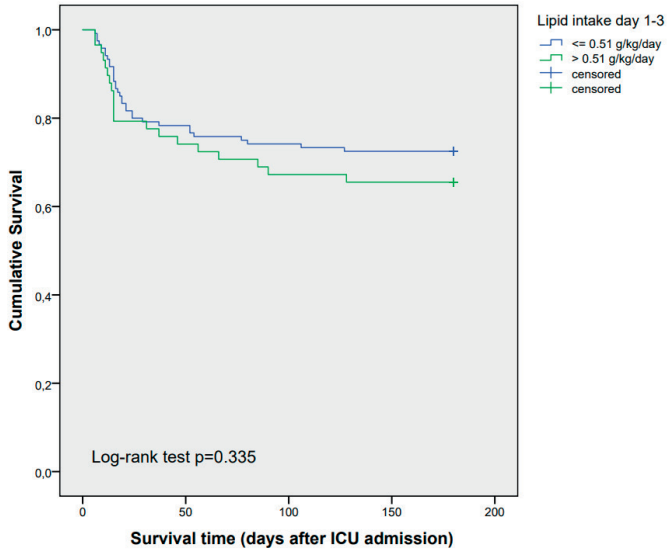
Cohort 1: cohort 2011-2015 ("Olthof cohort"); Cohort 2: cohort 2016-2018 ("Boot cohort");
RH = refeeding hypophosphatemia; N = number of patients; IQR = interquartile range; ICU = Intensive care unit; TDA = time to discharge alive;
a) p-values were calculated using the chi-square test, two sample t-test or Mann-Whitney U test where appropriate;
** p < 0.05.*

Supplement 5. Kaplan Meier curves (6-month mortality / macronutrient intake)

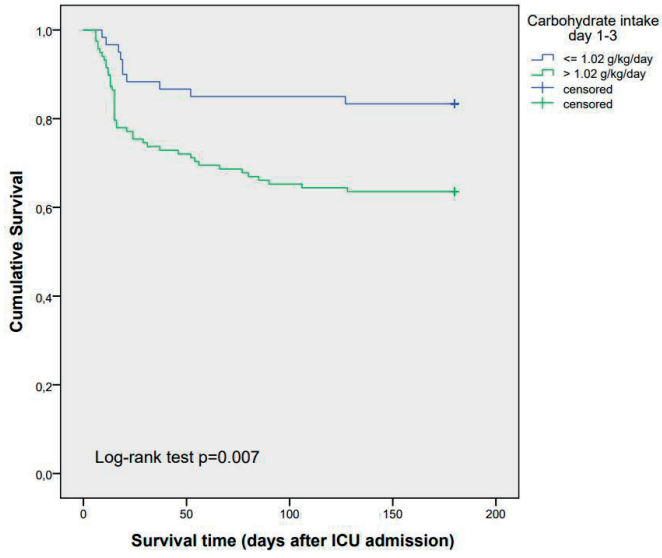
A) Six-month survival by Kaplan-Meier estimates for protein intake groups day 1-3



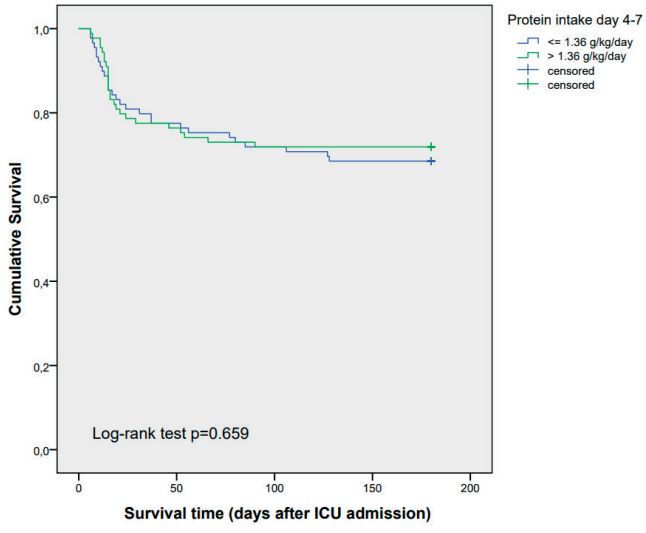
B) Six-month survival by Kaplan-Meier estimates for lipid intake groups day 1-3



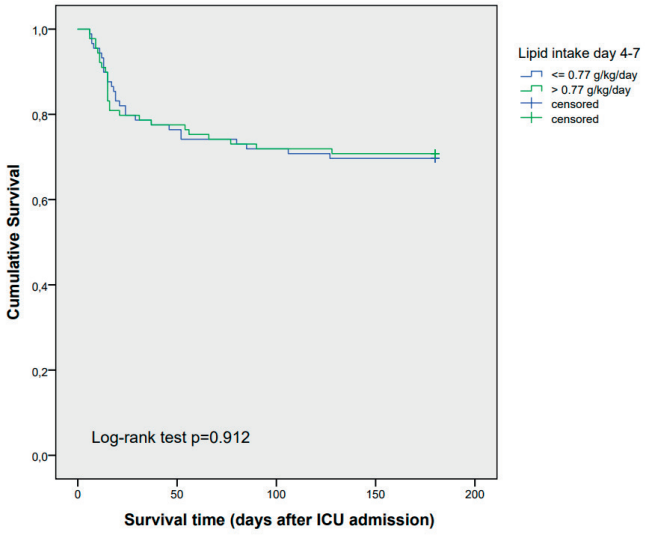
C) Six-month survival by Kaplan-Meier estimates for carbohydrate intake groups day 1-3



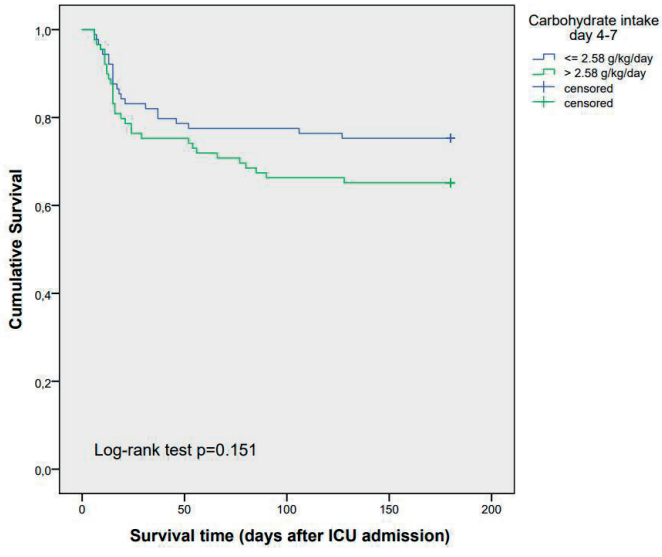
D) Six-month survival by Kaplan-Meier estimates for protein intake groups day 4-7



E) Six-month survival by Kaplan-Meier estimates for lipid intake groups day 4-7



F) Six-month survival by Kaplan-Meier estimates for carbohydrate intake groups day 4-7



Supplement 6. Univariable and multivariable regressions for secondary outcomes

A) ICU mortality (Cox proportional-hazards model)

Nutritional support days 1-3

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)	1.030 (0.997-1.064)	0.074	1.029 (0.994-1.064)	0.106
Gender (male)	1.349 (0.601-3.026)	0.468	1.270 (0.556-2.903)	0.570
BMI (kg/m^2)	0.985 (0.914-1.0620	0.697	1.004 (0.924-1.091)	0.924
APACHE II score on ICU admission	1.071 (1.006-1.141)	0.031*	1.082 (1.009-1.160)	0.028*
Protein intake (≤ 0.71 g/kg*day)	1.613 (0.740-3.513)	0.229	1.469 (0.510-4.230)	0.476
Lipid intake (≤ 0.51 g/kg*day)	0.958 (0.417-2.204)	0.920	0.877 (0.307-2.509)	0.807
Carbohydrate intake (≤ 1.02 g/kg*day)	1.870 (0.751-4.657)	0.179	1.568 (0.543-4.533)	0.406

Nutritional support days 4-7

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)	1.030 (0.997-1.064)	0.074	1.129 (0.994-1.281)	0.062
Gender (male)	1.349 (0.601-3.026)	0.468	0.215 (0.024-1.914)	0.168
BMI (kg/m^2)	0.985 (0.914-1.0620	0.697	0.844 (0.647-1.101)	0.212
APACHE II score on ICU admission	1.071 (1.006-1.141)	0.031*	1.046 (0.812-1.347)	0.726
Protein intake (≤ 1.36 g/kg*day)	0.694 (0.078-6.208)	0.744	3.782 (0.191-74.956)	0.383
Lipid intake (≤ 0.77 g/kg*day)	0.352 (0.039-3.152)	0.351	0.342 (0.027-3.871)	0.373
Carbohydrate intake (≤ 2.58 g/kg*day)	0.559 (0.062-5.005)	0.603	0.090 (0.004-1.888)	0.121

B) In-hospital mortality (Cox proportional-hazards model)

Nutritional support days 1-3

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)	1.045 (1.015-1.076)	0.003*	1.042 (1.011-1.074)	0.007*
Gender (male)	1.376 (0.704-2.689)	0.351	1.516 (0.750-3.065)	0.246
BMI (kg/m^2)	0.962 (0.901-1.027)	0.250	0.983 (0.913-1.059)	0.659
APACHE II score on ICU admission	1.059 (1.004-1.116)	0.034*	1.062 (1.000-1.128)	0.050
Protein intake (≤ 0.71 g/kg*day)	1.792 (0.945-3.399)	0.074	1.421 (0.586-3.444)	0.437
Lipid intake (≤ 0.51 g/kg*day)	1.257 (0.650-2.430)	0.496	1.100 (0.464-2.607)	0.828
Carbohydrate intake (≤ 1.02 g/kg*day)	2.115 (0.969-4.614)	0.060	1.830 (0.712-4.708)	0.210

Nutritional support days 4-7

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)	1.045 (1.015-1.076)	0.003*	1.060 (0.994-1.130)	0.078
Gender (male)	1.376 (0.704-2.689)	0.351	1.018 (0.174-5.958)	0.984
BMI (kg/m^2)	0.962 (0.901-1.027)	0.250	0.889 (0.717-1.101)	0.280
APACHE II score on ICU admission	1.059 (1.004-1.116)	0.034*	0.985 (0.835-1.163)	0.860
Protein intake (≤ 1.36 g/kg*day)	0.922 (0.186-4.569)	0.921	2.336 (0.313-17.465)	0.408
Lipid intake (≤ 0.77 g/kg*day)	0.476 (0.096-2.358)	0.363	0.477 (0.063-3.604)	0.473
Carbohydrate intake (≤ 2.58 g/kg*day)	0.749 (0.151-3.710)	0.723	0.367 (0.043-3.142)	0.360

C) Three-month mortality (Cox proportional-hazards model)

Nutritional support days 1-3

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)	1.039 (1.014-1.064)	0.001*	1.035 (1.009-1.061)	0.007*
Gender (male)	1.265 (0.710-2.253)	0.426	1.422 (0.777-2.602)	0.254
BMI (kg/m^2)	0.946 (0.892-1.003)	0.065	0.965 (0.904-1.031)	0.293
APACHE II score on ICU admission	1.061 (1.014-1.111)	0.010*	1.070 (1.016-1.128)	0.011*
Protein intake (≤ 0.71 g/kg*day)	2.075 (1.191-3.616)	0.010*	1.793 (0.842-3.815)	0.130
Lipid intake (≤ 0.51 g/kg*day)	1.322 (0.747-2.341)	0.338	0.966 (0.461-2.025)	0.927
Carbohydrate intake (≤ 1.02 g/kg*day)	2.625 (1.275-5.402)	0.009*	2.005 (0.845-4.757)	0.115

Nutritional support days 4-7

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age (years)	1.039 (1.014-1.064)	0.001*	1.031 (0.979-1.086)	0.249
Gender (male)	1.265 (0.710-2.253)	0.426	0.692 (0.160-3.001)	0.623
BMI (kg/m^2)	0.946 (0.892-1.003)	0.065	0.877 (0.726-1.059)	0.171
APACHE II score on ICU admission	1.061 (1.014-1.111)	0.010*	1.022 (0.887-1.178)	0.761
Protein intake (≤ 1.36 g/kg*day)	0.795 (0.165-3.827)	0.775	1.413 (0.225-8.863)	0.712
Lipid intake (≤ 0.77 g/kg*day)	0.709 (0.177-2.837)	0.627	0.702 (0.131-3.762)	0.680
Carbohydrate intake (≤ 2.58 g/kg*day)	0.638 (0.133-3.072)	0.575	0.381 (0.054-2.685)	0.333

HR = hazard ratio; 95% CI = 95% confidence interval; BMI = body mass index; APACHE II = Acute Physiology And Chronic Health Evaluation II; ICU = Intensive care unit.

D) Duration of mechanical ventilation (MV) & ICU and hospital length of stay (LOS), corrected for competing risk of death (linear regression with logarithmic transformation)

Nutritional support day 1-3	Duration of MV		ICU LOS		HOS LOS	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Age (years)	-0.002 (0.001)	0.099	-0.002 (0.002)	0.295	0.001 (0.002)	0.899
Gender (male)	-0.016 (0.037)	0.663	0.012 (0.043)	0.788	0.022 (0.047)	0.642
BMI (kg/m^2)	0.005 (0.004)	0.204	0.005 (0.004)	0.992	0.004 (0.004)	0.416
APACHE II score on ICU admission	0.003 (0.003)	0.290	0.001 (0.004)	0.731	-0.002 (0.004)	0.606
Protein intake (<= 0.71 g/kg*day)	-0.022 (0.050)	0.653	-0.016 (0.057)	0.780	-0.031 (0.061)	0.612
Lipid intake (<= 0.51 g/kg*day)	-0.015 (0.048)	0.750	-0.050 (0.056)	0.368	0.005 (0.061)	0.932
Carbohydrate intake (<= 1.02 g/kg*day)	0.028 (0.045)	0.539	0.028 (0.052)	0.586	0.047 (0.055)	0.389
Nutritional support day 1-3	**Duration of MV**		**ICU LOS**		**HOS LOS**	
	β (SE)	**p-value**	**β (SE)**	**p-value**	**β (SE)**	**p-value**
Age (years)	-0.003 (0.001)	0.038*	-0.002 (0.001)	0.293	0.001 (0.002)	0.758
Gender (male)	-0.012 (0.036)	0.735	0.016 (0.041)	0.703	0.036 (0.045)	0.421
BMI (kg/m^2)	0.007 (0.004)	0.097	0.007 (0.005)	0.987	0.003 (0.005)	0.517
APACHE II score on ICU admission	0.004 (0.003)	0.188	0.001 (0.004)	0.829	-0.001 (0.004)	0.738
Protein intake (<= 1.36 g/kg*day)	-0.093 (0.042)	0.128	-0.094 (0.048)	0.152	-0.107 (0.052)	0.139
Lipid intake (<= 0.77 g/kg*day)	-0.055 (0.040)	0.170	-0.060 (0.046)	0.190	-0.069 (0.050)	0.165
Carbohydrate intake (<= 2.58 g/kg*day)	0.052 (0.046)	0.255	-0.001 (0.053)	0.990	0.010 (0.056)	0.863

MV = mechanical ventilation; ICU = Intensive care unit; LOS = length of stay; HOS = hospital; SE = standard error; BMI = body mass index; APACHE II = Acute Physiology And Chronic Health Evaluation II;
** p-value <0.05.*

CHAPTER 6

6

PRospective Observational cohort Study of reached Protein and Energy Targets in general wards during the post-intensive care period: the PROSPECT-I study

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Abstract

Introduction

Nutrition plays an essential role in the recovery of critical illness. In the post-Intensive care unit (ICU) period, patients typically return to oral nutrition gradually. However, studies quantifying nutritional intake in the post-ICU hospitalization period are scarce and formal guidelines are lacking. This study aims to describe energy and protein intake in detail over the entire post-ICU hospitalization period and explore associations between protein intake and clinical outcomes.

Methods

A prospective observational single-center cohort study was conducted amongst post-ICU patients in general wards after a minimum ICU-stay of 72 hours and who received (par)enteral feeding for ≥24 hours in the ICU. Oral intake was assessed daily using food order lines and digital photography of meal leftovers. Other data, including amounts of (par)enteral nutrition, were collected from electronic medical records. The primary outcome was to identify energy and protein intake, and reached targets, in the post-ICU period. In addition, length of hospital stay after ICU discharge, readmission and mortality rates were compared between patients meeting protein targets or not.

Results

In total, 48 patients were included. Complete nutritional data of 34 patients were analyzed in the current study, adding up to a total number of 484 observational days, 1,681 photos and 6,634 food order lines. Inter-rater agreement was excellent (ICC 0.878). Overall mean energy and protein adequacy for all nutritional groups was 82.3% (SD 18.3) and 83.1% (SD 19.8). Only 51.2% of the study participants (n=21) reached overall >90% of prescribed protein targets during their entire post-ICU ward stay. The lowest intake was seen in the patient group with exclusively oral intake (median protein adequacy 75.5%), whereas patients with (supplemental) enteral nutrition (EN) all met >90% of their protein targets. Prescribed targets were below recommendations, and prescribed calories and proteins were neither ordered nor consumed. Discontinuation of EN resulted in immediate marked drops in energy (44.1%) and protein intake (50.7%). Subsequently, patients needed up to six days to reach protein targets again. No differences in clinical outcomes were observed.

Conclusion

Most patients did not meet energy and protein targets in the post-ICU hospitalization period. Nutrition performance was highly dependent on the

route of nutrition and was lowest among patients with oral intake only (despite of food fortification strategies and/or oral nutritional supplements). The best intake was observed in patients receiving (supplemental) EN. However, cessation of EN posed an immediate nutritional risk. No differences in clinical outcomes were found in this study. Our findings stress the need for follow-up studies to close the gap with individualized nutritional support in the post-ICU period to reach protein and energy targets.

Introduction

Nutrition plays a crucial role in the recovery of critical illness. Appropriate nutritional intake, in particular protein (≥ 1.3 g/kg*day (1)), in critically ill patients in the Intensive care unit (ICU) is associated with a decreased hospital length of stay (LOS), morbidity and mortality (2-6). However, critically ill patients are often unable to feed themselves. Therefore, enteral nutrition (EN) and/or parenteral nutrition (PN) are regularly administered in the ICU (1). In the (post-ICU) recovery period from critical illness, it is expected that patients return to oral nutrition gradually. This transition is often combined with supplemental EN or PN. Furthermore, food fortification strategies, such as energy- and protein-enriched foods or oral nutrition supplements (ONS), are frequently used. Nevertheless, formal guidelines for the dynamic nutritional targets of post-ICU patients are lacking. Guidelines that may be suitable for these patients recommend a caloric intake of 25-30 kcal/kg*day and a protein intake of about 1.5g/kg*day (7-8). However, during the recovery phase of critical illness, patients' metabolic targets and physical mobility increase significantly (9-12). Thus, it may be suggested that their energy expenditure will exceed the recommended energy and protein intake. Inadequate nutrition in this phase will lead to poor recovery (13). Therefore, optimizing protein and energy intake is essential to attenuate further loss of lean body mass and promote recovery of physical functioning and quality of life (10-12).

Current literature assessing nutritional performance in the post-ICU period in general wards is scarce (14). Ridley *et al.* demonstrated that energy and protein intake remained below predicted targets (15). The lowest intake was observed in the patients with exclusively oral intake, while patients with total EN did not demonstrate a deficit in energy and protein intake. This observation is in line with Moisey *et al.,* who examined the nutritional intake of 19 critically ill patients in the first week after extubation (16). A study conducted among 37 patients with moderate traumatic brain injury by Chapple *et al.* showed similar results, although energy and protein deficits in patients on solely EN were also demonstrated (17). Collectively, these studies suggest that nutritional follow-up and strategies to enhance intake during the phase after critical illness are necessary, although the evidence is limited (14,27,18). Sample sizes were small, nutritional intake was not assessed daily, and PN was not considered (15,17). Furthermore, it is unknown whether nutritional intake in the post-ICU hospitalization period is associated with clinical outcomes, such as length of hospital stay, morbidity and mortality. In a multicenter trial outside critical care, it has been demonstrated that individualized nutritional support results in enhanced energy and protein intake and lowers the risk of 30-day adverse outcomes and mortality (14,19).

This present study describes a complete representation of the energy and protein intake over the entire post-ICU hospitalization period, with a specific interest in energy and protein intake and reached targets between patients with different nutritional routes (oral, EN and/or PN). Secondary study endpoints included length of hospital stay after ICU discharge, discharge destinations, readmission, and mortality rates. We hypothesize that adequate nutrition in the post-ICU period may positively impact clinical outcomes. The findings from the proposed work will yield new insight into nutritional intake during the post ICU-period.

Materials and methods

Study design

A prospective observational single-center cohort study was conducted from 6 May 2019 to 16 March 2020 in patients who were discharged from a mixed medical-surgical ICU to a general ward of Gelderse Vallei hospital (ZGV, Ede, The Netherlands). Study inclusions were ended unexpectedly early due to the outbreak of the COVID-19 pandemic.

Study participants

Critically ill adult patients (aged ≥18 years) who were ready for ICU discharge after an ICU-stay of ≥72 hours and who received (par)enteral feeding for ≥24 hours during ICU stay were eligible for inclusion. Any patient who received exclusively oral nutrition during ICU stay was excluded, since we were interested in patients who underwent a transition in nutritional mode. Moreover, patients on exclusive oral nutrition were thought to have lower disease acuity, and it is likely that these patients can ramp-up oral feeding more rapid after ICU discharge than patients on (prolonged) medical nutrition.

Additionally, anyone who was not discharged to a general ward in our hospital was excluded, as were patients who had a life-expectancy of <48 hours. Until August 2019, patients who were discharged to a non-surgical ward were excluded as well, as there was no permission for study assessments in these wards at the start of the study (hereafter indicated with "non-PROSPECT ward"). After obtaining informed consent from the patient or legal representative, eligible patients were enrolled in consecutive order.

Clinical data collection

Data collection from the electronic Patient Data Management System (PDMS) included patient characteristics (age, gender, anthropometry, comorbidities), admission type, several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS II), Nutrition Risk In Critically ill (NUTRIC)), and outcome parameters, such as length of

ICU and hospital stay (LOS), 3-, 6- and 12-month readmission and mortality rates. On the day of ICU and hospital discharge, start and end of study assessments were performed, including assessment of swallowing function and physical performance (using the Medical Research Council (MRC) scale for global muscle strength evaluation and Chelsea Critical Care Physical Assessment tool (CPAx)).

Data extraction was performed using queries searching the ICU PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (NeoZis; MI Consultancy, Katwijk, The Netherlands). The National Population Register was consulted for death records. Data verification was conducted manually. All parameters of interest, except for assessment of physical performance, had been routinely collected during standard clinical care, and therefore imposed no burden or risk to patients.

Nutritional assessment

The study started on the day of ICU discharge (day 0). Days were defined as calendar days.

From the first study day onwards until hospital discharge, type of nutrition (oral, EN, PN, or a combination thereof) as well as total energy (in kcal/day) and protein (in g/day) intake were recorded daily (see **Supplement 1**). Small amounts of food or sips of water to assess swallowing function were not considered oral intake. Quantifications of nutrition were used to calculate the percentage of reached energy and protein targets (hereafter indicated with "adequacy"), as set by the dieticians. Timing and reason of discontinuation or start of (par)enteral nutrition was recorded, as well as removal of a feeding tube or central venous catheter. Study assessments and data collection were stopped when death was imminent. The intake on (ICU and hospital) discharge days were excluded from final nutritional analyses.

In case of readmission to the ICU, only the nutritional data after ICU readmission were analyzed.

Assessment of oral intake

To quantify oral nutrition, pictures of meal leftovers were assessed. All study participants were discharged from the ICU with a digital camera attached to their beds and study placemats on their meal trays. Post-meal photos were taken by general ward nurses and food service assistants. Two researchers (RSB and LD/SM) analyzed these pictures independently after the patient finished study participation. These pictures were compared to pre-meal images of serving portions, which were made by one researcher (NS) under precisely similar conditions before the start of the study (20). The amount of food consumed was graded with 0 (indicating nothing consumed) - 0.25 - 0.375 - 0.5 -

0.625 - 0.875 - or 1 (indicating entire meal consumed). Discrepancies in the assessment were resolved by discussion. In case of missing products in the pictures, missing data were extrapolated using intake data of that specific meal or day. If this was not possible due to too many missings, data were imputed using nursing report sheets and digital food record charts. If this could not be obtained, missing mealdata were excluded from nutritional analyses.

Oral intake assessments were compared to the database with food order lines from At Your Request® (AYR). AYR is a hospital meal service offering patients the possibility to order from a menu card throughout the day between 7 a.m. and 7 p.m. by placing a telephone call (21). The operators from the call center are aware of the patients' diets and might help them choose from the menu. Kitchen staff prepare and serve the ordered food in standardized serving sizes, which are delivered within 45 minutes to the patients. All food orders (per patient per day) are automatically stored in the Menu Management System, including information about macronutrients (calories and proteins).

Patients, hospital staff, family and visitors were kindly asked to list all additional nutrition not ordered from AYR on a food intake chart.

Assessment of (par)enteral nutrition

Data regarding calories and proteins from administered (par)enteral nutrition were collected manually from the PDMS.

Calculation of targets

Energy and protein targets were calculated by the dieticians using the Food and Agricultural Organization and World Health Organization (22) formulas, adapted for specific patient groups (such as chronic kidney disease or dialysis) according to the local hospital protocol for nutritional support (**see Supplement 2**)(22). Patient's weight on ICU admission was used for these calculations, as measured using bedscales. Weight of patients with a Body mass index (BMI) of <18.5 or >27 kg/m^2 was adjusted to ideal body weight (IBW) at a BMI of 18.5 or 27 kg/m^2. Energy and protein targets on the day of ICU and hospital discharge were adjusted for the actual time spent in the ICU and ward these days, respectively.

The role of the dieticians in this study was not different from general practice in our hospital. Nutritional prescriptions of post-ICU patients are reviewed two times per week by dieticians. In case of insufficient oral intake, patients were provided with dietician advice to match preferences and needs, and/or prescribed food fortification strategies, ONS or tube feeding.

Study outcomes

The primary objective of this study was to assess energy and protein intake expressed as a percentage of calculated targets (adequacy) between patients with oral, enteral, parenteral, or combined nutrition in general wards during the post-ICU hospitalization period.

The secondary objective was to explore differences in outcomes such as length of hospital stay after ICU discharge, discharge destinations, readmission, and mortality rates between protein intake groups. Protein intake groups were based on achieving less or more than 90% of the protein targets during ward stay. Clinical outcomes of the low (<90% of targets) versus the high (>90%) intake groups were compared. A composite endpoint of unfavourable outcome was composed of hospital readmission within six months or 6-month mortality.

Statistical analysis

Discrete variables were reported as proportions. Continuous data were expressed in means including standard deviations (SD) or, in the case of non-parametric data, as medians with interquartile ranges (IQR). P-values for continuous outcome variables were calculated using paired t-tests, two-sample t-tests or one-way ANOVA, or in case of non-normal distribution, Wilcoxon signed-rank, Mann-Whitney U or Kruskal Wallis tests where appropriate. Crosstabs were assessed using the Chi-Square test; the Fisher Exact test was used when cell counts were lower than 5. P-values below 0.05 were considered statistically significant. P-values <0.10 were considered trends. An intraclass correlation coefficient (ICC) was computed to evaluate agreement between two researchers in the assessment of digital pictures to quantify oral intake (two-way random effects model). Inter-rater agreement was considered poor with an ICC <0.4, fair when $0.4 \leq ICC < 0.6$, good when $0.6 \leq ICC < 0.8$ and excellent when ICC was ≥ 0.8.The composite endpoint (6-month hospital readmission or mortality) was assessed by Kaplan Meier curves and Cox Proportional Hazards Regression Analysis. All relevant variables based on current literature were included in the univariable Cox regression analysis. Furthermore, variables with a p-value <0.10 and which were deemed clinically relevant were included in multivariable Cox regression analyses.

All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA; 2016). Normality was assessed numerically and graphically (visual inspection of histograms and Q-Q plots).

Ethical approval

The ethical approval committee approved the study of ZGV (study protocol number 1810-181).

Results

A total of 626 patients were discharged from our ICU during the study period, of whom 121 were eligible for inclusion (see **Figure 1**). Of these, 48 patients were enrolled in the study.

The baseline characteristics of the included and analyzed patients are summarized in **Table 1**. The patient group who received (supplemental) PN (n=3) at ICU discharge consisted of surgical patients only (p=0.06). A trend toward lower APACHE II, SOFA, SAPS II and NUTRIC scores (p<0.01) was seen in this patient group.

Table 1. Baseline characteristics

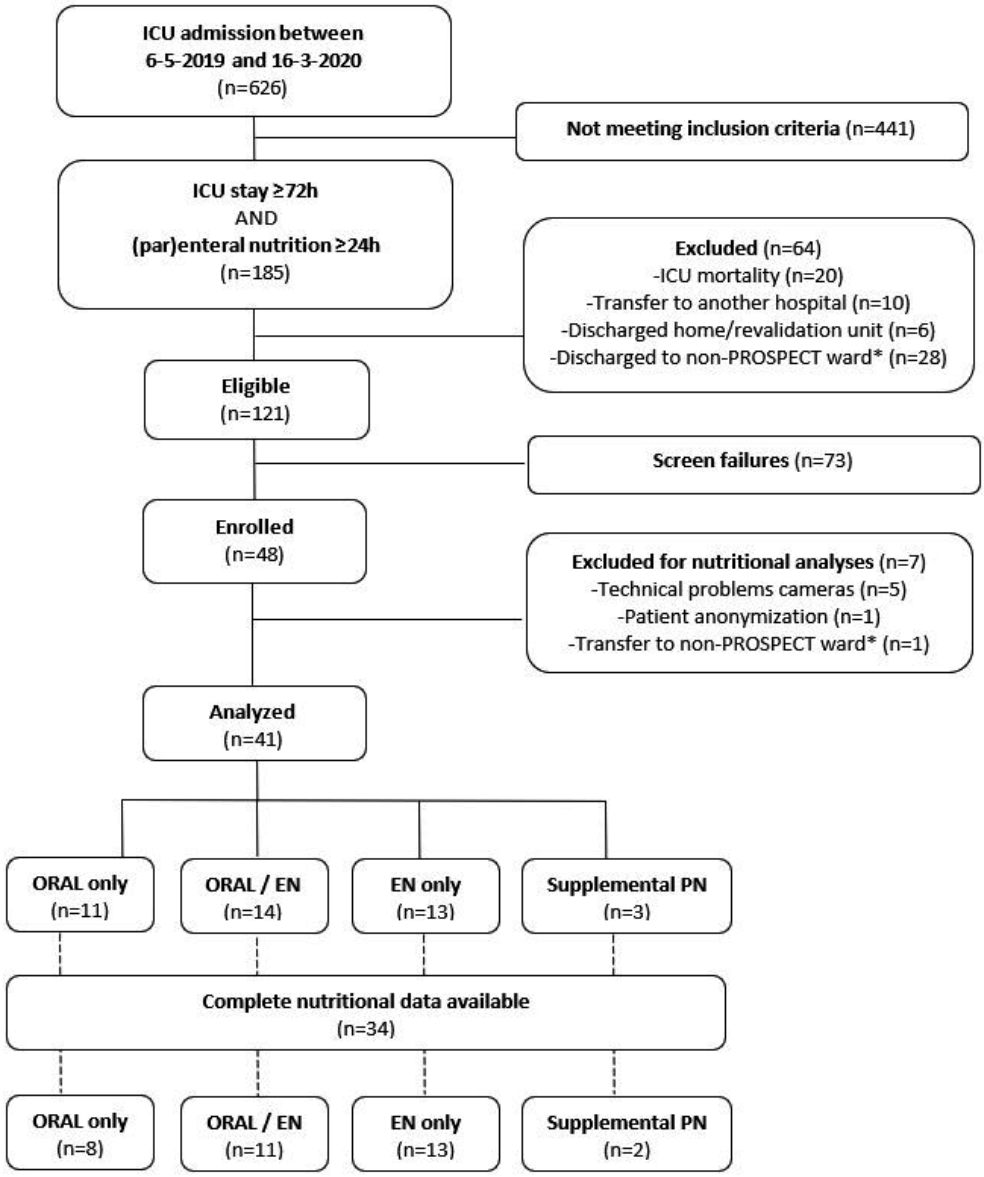
		All patients	ORAL only[a)]	ORAL/ EN[a)]	EN only[a)]	PN ± EN ± ORAL[a)]	p-value[b)]
		(n=41)	(n= 11)	(n=14)	(n=13)	(n=3)	
Gender (male)	*N (%)*	19 (46.3)	5 (45.5)	6 (42.9)	6 (46.2)	2 (66.7)	0.517
Age (years)	*mean (SD)*	70.8 (11.4)	70.0 (10.9)	71.3 (10.9)	70.9 (13.9)	70.7 (9.5)	0.908
BMI on ICU admission (kg/m^2)	*mean (SD)*	26.7 (6.0)	27.8 (7.3)	24.6 (6.0)	27.3 (4.4)	29.2 (7.0)	0.241
APACHE II score on ICU admission	*mean (SD)*	20.4 (6.7)	23.2 (6.7)	20.4 (7.6)	19.2 (5.4)	15.3 (4.7)	0.348
SOFA score on ICU admission	*mean (SD)*	6.6 (2.8)	7.4 (3.8)	6.6 (2.5)	6.3 (2.3)	5.0 (2.0)	0.770
SAPS II score	*mean (SD)*	43.2 (13.4)	46.3 (17.5)	43.9 (11.9)	43.7 (9.8)	27 (10)	0.210
NUTRIC score	*mean (SD)*	5.0 (1.4)	5.4 (1.9)	4.7 (1.1)	5.2 (1.4)	4.0 (1.0)	0.486
Admission type (non-surgical)	*N (%)*	23 (56.1)	9 (81.8)	9 (64.3)	5 (38.5)	0 (0)	0.066

N = number of patients; SD = standard deviation; BMI = body mass index; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; SAPS II = Simplified Acute Physiology Score; NUTRIC = Nutrition Risk in Critically ill;

[a)] Nutritional route at ICU discharge: ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition;

[b)] p-values were calculated using the Fisher Exact test or one-way ANOVA where appropriate.

Figure 1. Study flowchart



*ICU = Intensive care unit; ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition; *non-PROSPECT ward: patients who were discharged to a medical ward could only be included from August 2019 onwards, as there was no permission for study assessments in these wards at the start of the study.*

Nutritional assessment

Due to technical problems with photo cameras, the nutritional data of five patients could not be analyzed, and two patients were excluded from further analyses due to patient anonymization and transferal to a non-PROSPECT ward. An overview of nutritional parameters of the 41 evaluable patients is depicted in **Table 2**. From 34 patients (82.9%), nutritional intake during the entire study participation could be analyzed. From seven patients (17.0%) incomplete data was available (median 4 [IQR 2-9] days); only twenty-eight out of 60 days could be analyzed due to missing data. The number of observational days after ICU discharge (and thus length of ward stay) was median 12 [IQR 8-15] days. No food record charts that reported food not registered by AYR, such as food brought in by family members, were retrieved. A total number of 484 study days were analyzed, including 1,681 post-meal photos and 6,634 order lines from AYR. There was excellent agreement between the two researchers in the assessment of pictures to quantify oral intake (ICC 0.878). Mean difference was 0.7 kilocalories and 0.02 grams of protein per product ordered.

Nutritional routes at ICU discharge varied between oral intake only (n=11 (26.8%); 123 study days), EN only (n=13 (31.7%); 177 days), combined oral/EN (n=14 (34.1%); 152 days) or supplemental PN (n=3 (7.3%); 32 days). At hospital discharge, most patients had exclusively oral intake (n=28; 68.3%). Ten patients (24.4%) were discharged with (supplemental) EN, and one patient (2.4%) with supplemental PN.

Table 2. Nutritional data - overview

		All patients (n=41)	ORAL only[a)] (n= 11)	ORAL/EN[a)] (n=14)	EN only[a)] (n=13)	PN ± EN ± ORAL[a)] (n=3)	p-value[b)]
Nutritional route *at hospital discharge*	*N (%)*						<0.001*
ORAL only		28 (68.3)	11 (100)	10 (71.4)	6 (46.2)	1 (33.3)	
ORAL+EN		7 (17.1)	0 (0)	4 (28.6)	3 (23.1)	0 (0)	
EN		3 (7.3)	0 (0)	0 (0)	3 (23.1)	0 (0)	
PN+ORAL		1 (2.4)	0 (0)	0 (0)	0 (0)	1 (3.3)	
Not appropriate (in-hospital death)		2 (4.9)	0 (0)	0 (0)	1 (7.7)	1 (3.3)	
Swallowing function at ICU discharge	*N (%)*						0.012*
Good		28 (68.3)	11 (100)	11 (78.6)	3 (23.1)	3 (100)	
Moderate		10 (24.4)	0 (0)	2 (14.3)	8 (61.5)	0 (0)	
Bad		3 (7.3)	0 (0)	1 (7.1)	2 (15.4)	0 (0)	
Jejunal feeding tube at ICU discharge (yes)	*N (%)*	4 (9.8)	0 (0)	1 (7.1)	2 (15.4)	1 (33.3)	0.024*
Energy target in ward (kcal/kg IBW*day)	*median [IQR]*	27.8 [26.3-29.3]	28.2 [26.8-30.6]	27.9 [26.4-30.4]	26.9 [25.9-28.3]	31 [28-42]	0.163
Energy intake (kcal/kg IBW*day[c)])	*mean (SD)*	24.7 (7.5)	24.2 (6.2)	25.9 (9.8)	24.1 (6.4)	23.7 (7.1)	0.963
Adequacy to target (%)		82.3 (18.3)	81.7 (15.9)	82.5 (19.5)	85.9 (19.8)	69.9 (14.3)	0.604
Protein target in ward (g/kg*day)	*N (%)*						0.078
1,2 g/kg*day		5 (12.2)	3 (27.3)	0 (0)	1 (7.7)	1 (33.3)	
1,2-1,5 g/kg*day		12 (29.3)	4 (36.4)	4 (28.6)	4 (30.8)	0 (0)	
1,5 g/kg*day		24 (58.5)	4 (36.4)	10 (71.4)	8 (61.5)	2 (66.7)	
Protein intake (g/kg IBW*day[c)])	*mean (SD)*	1.25 (0.38)	1.15 (0.35)	1.31 (0.45)	1.27 (0.33)	1.22 (0.47)	0.864
Adequacy to target (%)		83.1 (19.8)	79.1 (14.5)	82.8 (21.9)	85.6 (20.8)	80.9 (30.1)	0.752
Overall averaged energy adequacy >90%	*N (%)*	20 (48.8)	4 (36.4)	8 (57.1)	8 (61.5)	0 (0)	0.311
Overall averaged energy adequacy >100%	*N (%)*	11 (26.8)	3 (27.3)	5 (35.7)	3 (23.1)	0 (0)	0.778
Overall averaged protein adequacy >90%	*N (%)*	21 (51.2)	3 (27.3)	8 (57.1)	8 (61.5)	2 (66.7)	0.376
Overall averaged protein adequacy >100%	*N (%)*	14 (34.1)	2 (18.2)	6 (42.9)	5 (38.5)	1 (33.3)	0.358

N = number of patients; IQR = interquartile range; SD = standard deviation; ICU = intensive care unit; IBW = ideal bodyweight;

a) Nutritional route at ICU discharge: ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition;

b) p-values were calculated using Fisher Exact test, Kruskal Wallis test or one-way ANOVA where appropriate;

c) average during hospital stay after ICU discharge; all nutritional routes (oral, EN, PN, or mixed);

** p-value <0.05.*

Dietician energy targets for the PN group were, on average, higher than the other nutritional groups, although not statistically significant (p=0.071), mainly due to a single patient whose target was set at 3,300 kcal/day (42 kcal/kg IBW*day) to compensate for intestinal losses. Most patients were prescribed a protein target of 1.5 g/kg*day (n=24; 58.5%). Mean energy and protein intake averaged over all study days for all nutritional groups was 24.7 (standard deviation (SD) 7.5) kcal/kg IBW*day and 1.25 (SD 0.38) g/kg IBW*day respectively, corresponding to 82.3% (SD 18.3) and 83.1% (SD 19.8) of reached targets, respectively. Twenty-one patients (51.2%) had overall protein adequacy above 90% during their ward stay after ICU discharge. Of note, all patients (100%) with oral nutrition, received food fortification and/or ONS.

Oral nutrition only

The patients with oral nutrition only at ICU discharge (n=11) had a median overall energy intake during ward stay of 22.3 [IQR 18.8-29.3] kcal/kg IBW*day, corresponding to median adequacies of 82.2% [IQR 66.4-100] (p=0.037) (**Table 3A, Supplement 4B**). Four patients (36.4%) had an average overall energy adequacy above 90%. Of note, in patients not reaching energy targets (adequacy <90%; intake median 19.7 [IQR 17.9-22.1] kcal/kg IBW*day), the amount of energy ordered was significantly below target prescriptions (median 25.4 [IQR 23.8-26.2] versus 28.1 [26.3-29.4] kcal/kg IBW*day; p=0.018) (**Table 3B**).

The median protein intake was 1.07 [IQR 0.90-1.35] g/kg IBW*day. This corresponded to median adequacies of 75.5% [IQR 69.1-94.7]. Three (27.3%) patients had an overall average adequacy of >90% regarding protein intake. Also, in patients not reaching protein prescriptions (adequacy <90%; intake median 0.92 [IQR 0.84-1.13] g/kg IBW*day], the amount of protein ordered was statistically significant less than prescribed (median 1.17 [IQR 1.15-1.27] versus 1.33 [1.23-1.50] g/kg IBW*day; p=0.018).

Details of nutritional intake in patients with adequacies below 100% are shown in **Supplement 3**.

Table 3. Nutritional data - patients with ORAL nutrition ONLY (n=11)
A. All patients with ORAL nutrition only (n=11)

		Target	Ordered	p-value[a)]	Intake	p-value[a)]	Adequacy (%)
Energy (kcal/kg IBW*day)	*median [IQR]*	28.2 [26.8-30.6]	26.3 [25.1-31.2]	0.646	22.3 [18.8-29.3]	0.037*	82.2 [66.4-100.0]
Protein (g/kg IBW*day)	*median [IQR]*	1.36 [1.23-1.49]	1.27 [1.16-1.43]	0.285	1.07 [0.90-1.35]	0.093	75.5 [69.1-94.7]

B. Patients with energy and/or protein adequacy <90%

		Target	Ordered	p-value[a)]	Intake	p-value[a)]	Adequacy (%)
Energy (kcal/kg IBW*day) (n=7)	*median [IQR]*	28.1 [26.3-29.4]	25.4 [23.8-26.2]	0.018*	19.7 [17.9-22.1]	0.018*	70.1 [63.0-81.2]
Protein (g/kg IBW*day) (n=8)	*median [IQR]*	1.33 [1.23-1.50]	1.17 [1.15-1.27]	0.018*	0.92 [0.84-1.13]	0.018*	73.8 [68.2-76.4]

IBW = ideal bodyweight; IQR = interquartile range;
[a)] p-values were calculated using the one sample t-test and sign test where applicable (after calculating deficits in nutritional orders and intake compared to target);
** p-value <0.05.*

Transition from (supplemental) EN to oral nutrition only

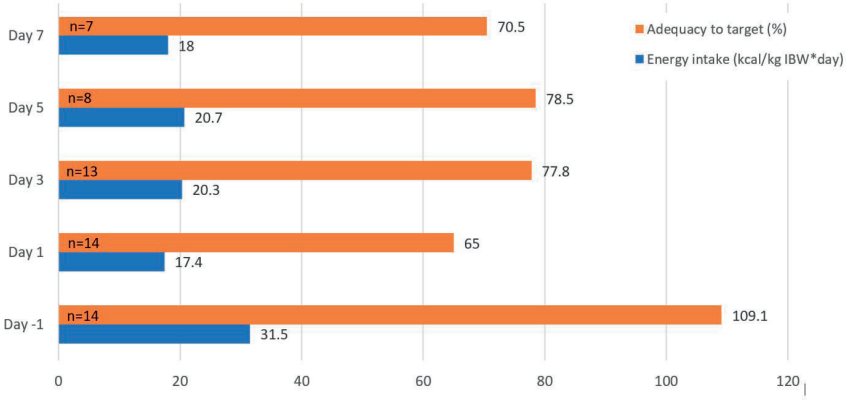
During ward stay, 16 patients (53.3%) went through a transition from (supplemental) EN to exclusively oral nutrition. These patients received median 3 [IQR 1-5] days of (supplemental) EN before discontinuation (**Table 4**). Reasons to stop EN included (supposed) sufficient oral intake (n=13), inadvertent removal of feeding tube (n=2), or patient refusal (n=1). Median overall averaged energy and protein adequacy before the stop of EN was 97.3% [IQR 77.3-119.8] and 91.5% [78.0-142.4], respectively. The performance dropped to an overall average adequacy of median 76.0% [IQR 63.0-88.9] and 75.4% [55.2-101.7] after the discontinuation of EN support. A statistically significant increase in energy and proteins ordered was seen after discontinuation of enteral feeding (p=0.008), although this was not enough to reach prescribed targets (median adequacy to energy and protein target: 81.8% and 90.4%, respectively).

The largest drop in intake was seen at day 1 after discontinuation of EN (median energy intake 17.4 [IQR 15.9-31.0] kcal/kg IBW*day (adequacy 65.0% [50.3-102.0]); median protein intake 0.97 [0.80-1.52] g/kg IBW*day (adequacy 60.6% [53.6-104.3])) (**Figure 2**). After this, an increase in energy intake was seen until day 6 to median 22.3 [16.5-28.4] kcal/kg IBW*day (adequacy median 75.2% [IQR 57.0-112.2]) and protein intake to 1.36 [0.66-1.64] g/kg IBW*day (adequacy median 103.2% [44.1-118.6]). A second drop of energy and protein intake was seen at day 7 in the patients who were not discharged from the hospital yet, as shown in **Table 4**, although not statistically significant (p=0.068 and 0.144, respectively).

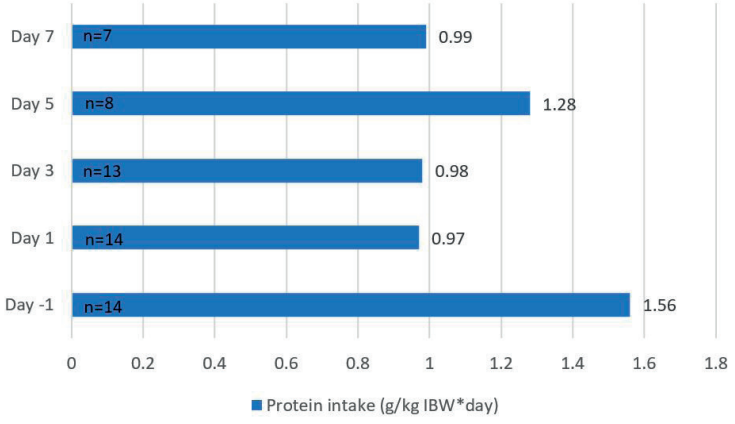
Separate analyses were performed for patients with <100% protein adequacy both before and after discontinuation of EN; these results are shown in **Supplement 6**.

Figure 2. Discontinuation of enteral nutrition in the post-Intensive care unit hospitalization period

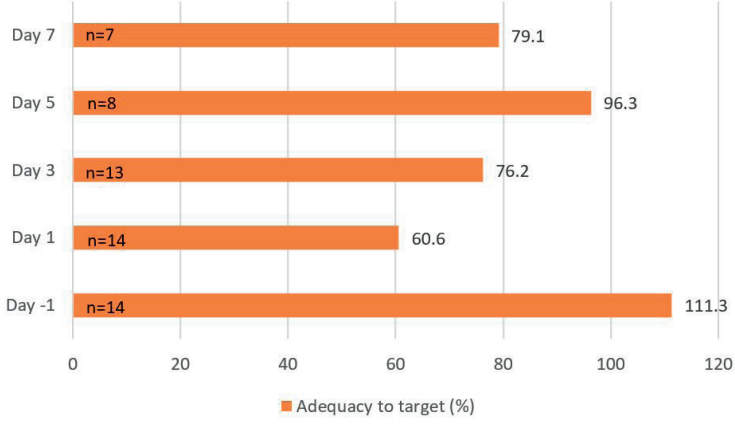
A.



B.



C.



Day -1 = day before discontinuation; day 1 = first day after discontinuation; IBW = ideal bodyweight.

Table 4. Nutritional data - transition from enteral feeding to oral nutrition ONLY during ward stay (n=16)

A) Overview (n=16)

Duration of (supplemental) EN (full days)	*median [IQR]*	3 [1-5]
Full observational days after stop EN	*median [IQR]*	6 [4-12]
Energy target in ward (kcal/kg IBW*day)	*median [IQR]*	26.8 [25.9-29.0]
Protein target in ward (g/kg*day)	*N (%)*	
1,2 g/kg*day		0 (0)
1,2-1,5 g/kg*day		6 (37.5)
1,5 g/kg*day		10 (62.5)
Reason to stop EN	*N (%)*	
Accidental removal of FT		2 (12.5)
Sufficient intake		13 (81.3)
Patient refusal/complaints		1 (6.3)

B) All observational days averaged (n=16)

		Before stop EN	**After stop EN**	**p-value[a)]**
Energy intake	*median [IQR]*			
Ordered (kcal/kg IBW*day)		13.5 [6.5-24.8]	23.6 [18.8-29.9]	0.008*
Adequacy to target (%)		44.0 [23.5-89.8]	81.8 [69.8-109.2]	0.008*
Intake (kcal/kg IBW*day)		27.6 [19.3-33.7]	20.9 [17.7-31.0]	0.441
Contribution EN (%)		52.7 [46.4-83.7]	NA	NA
Adequacy to target (%)		97.3 [77.3-119.8]	76.0 [63.0-88.9]	0.463
Protein intake	*median [IQR]*			
Ordered (g/kg IBW*day)		0.62 [0.23-1.14]	1.37 [0.94-1.61]	0.008*
Adequacy to target (%)		41.5 [18.8-79.1]	90.4 [62.9-116.5]	0.008*
Intake (g/kg IBW*day)		1.27 [0.94-1.79]	1.12 [0.82-1.60]	0.374
Contribution EN (%)		60.7 [48.0-87.7]	NA	NA
Adequacy to target (%)		91.5 [78.0-142.4]	75.4 [55.2-101.7]	0.075

IQR = interquartile range; N= number of patients; EN = enteral nutrition; IBW = ideal bodyweight; FT = feeding tube

C) Comparisons between observational days

		Day -1	Day 1	p-value[a)]	Day 3	p-value[a)]	Day 5	p-value[a)]	Day 6	p-value[a)]	Day 7	p-value[a)]
		(n=14)	(n=14)		(n=13)		(n=8)		(n=7)		(n=7)	
Energy	*median [IQR]*	31.5 [24.8-37.4]	17.4 [15.9-31.0]	0.018*	20.3 [14.0-28.5]	0.046*	20.7 [19.4-38.9]	0.273	22.3 [16.5-28.4]	0.068	18.0 [13.3-21.0]	0.068
Adequacy		109.1 [85.1-139.7]	65.0 [50.3-102.0]	0.004*	77.8 [56.0-108.8]	0.248	78.5 [71.9-129.8]	0.273	75.2 [57.0-112.2]	0.249	70.5 [45.1-83.1]	0.116
Protein	*median [IQR]*	1.56 [1.22-2.02]	0.97 [0.80-1.52]	0.028*	0.98 [0.62-1.45]	0.046*	1.28 [0.76-1.80]	0.273	1.36 [0.66-1.64]	0.465	0.99 [0.67-1.40]	0.144
Adequacy		111.3 [78.2-149.6]	60.6 [53.6-104.3]	0.012*	76.2 [47.4-109.4]	0.062	96.3 [53.4-118.0]	0.273	103.2 [44.1-118.6]	0.463	79.1 [46.0-101.4]	0.173

*Day 0 = stop EN; energy intake in kcal/kg IBW*day; protein intake in g/kg IBW*day; adequacy = adequacy to target (%);*

[a)] *p-values were calculated using the Wilcoxon signed rank test; observational days were compared to day -1 (=day before discontinuation of EN);*

** p-value <0.05.*

The patient group who discontinued EN because of (supposed) sufficient intake (n=13) had overall median energy and protein adequacies of 99.8% [IQR 66.4-133.5] and 95.4% [78.8-155.7] before discontinuation, although five of them (38.5%) had an overall median protein adequacy <90% (**Supplement 6**).

After discontinuation, the median average overall energy and protein adequacies until hospital discharge were 77.0% [IQR 63.2-88.4] and 75.9% [53.6-100.6], respectively, with the best adequacy seen on day 5.

Hospital discharge with (par)enteral nutrition

Ten patients were discharged from the hospital with (supplemental) EN and one with supplemental PN. This patient group reached overall energy and protein adequacies above 95% during their post-ICU ward stay, as shown in **Table 5**.

Table 5. Nutritional data - patients with enteral nutrition until hospital discharge (n=10)

Energy target in ward (kcal/kg*day)	*median [IQR]*	27.3 [26.2-29.0]
Energy intake, overall		
Ordered (kcal/kg IBW*day) (n=7)		11.5 [4.5-22.6]
Intake (kcal/kg IBW*day)		26.3 [24.8-31.1]
Contribution EN (%)		89.8 [63.1-100]
Adequacy to target (%)		98.2 [94.2-100]
Protein target in ward (g/kg*day)	*N (%)*	
1,2 g/kg*day		1 (10)
1,2-1,5 g/kg*day		2 (20)
1,5 g/kg*day		7 (70)
Protein intake, overall	*median [IQR]*	
Ordered (g/kg IBW*day) (n=7)		0.47 [0.22-1.16]
Intake (g/kg IBW*day)		1.50 [1.40-1.63]
Contribution EN (%)		92.4 [63.9-100]
Adequacy to target (%)		100 [98.1-100]

IQR = interquartile range; N= number of patients; IBW = ideal bodyweight; EN = enteral nutrition; Adequacy was reported at a maximum of 100%.

Subgroup analyses: overall protein adequacy <90% and >90%

Subgroup analyses were performed based on achievement of less or more than 90% of protein targets (**Table 6**). The low intake (<90%) group had statistically significant higher mean SOFA (8.1 (SD 1.5) versus 5.2 (SD 2.3), p=0.001) and NUTRIC scores (5.5 (SD 1.5) versus 4.5 (SD 1.2), p=0.022) compared to the high intake group (>90% of targets reached). Of note, all patients who were discharged with (supplemental) (par)enteral nutrition achieved >90% of protein targets during their ward stay.

Table 6. Patients with overall <90% and >90% protein adequacy (all nutritional routes)

		Overall protein adequacy		p-value[a)]
		<90%	>90%	
		(n=20)	(n=21)	
Age (years)	*median [IQR]*	75 [68-81]	72 [61-79]	0.411
Gender (male)	*N (%)*	13 (65)	6 (28.6)	0.019*
Type of admission (non-surgical)	*N (%)*	11 (55)	12 (57.1)	0.890
BMI on ICU admission (kg/m^2)	*mean (SD)*	28.0 (6.0)	25.4 (5.7)	0.158
APACHE II score on ICU admission	*mean (SD)*	21.9 (7.4)	19.0 (5.7)	0.179
SOFA score on ICU admission	*mean (SD)*	8.1 (1.5)	5.2 (2.3)	0.001*
SAPS II score	*mean (SD)*	45.1 (13.5)	41.4 (13.4)	0.538
NUTRIC score	*mean (SD)*	5.5 (1.5)	4.5 (1.2)	0.022*
Nutritional route *at ICU discharge*	*N (%)*			0.376
ORAL only		8 (40)	3 (14.3))	
ORAL+EN		6 (30)	8 (38.1)	
EN only		5 (25)	8 (38.1)	
PN ± EN ± ORAL		1 (5)	2 (9.6)	
Nutritional route *at hospital discharge*	*N (%)*			0.006*
ORAL only		19 (95)	9 (42.9)	
ORAL+EN		0 (0)	7 (33.3)	
EN only		0 (0)	3 (14.1)	
PN ± EN ± ORAL		0 (0)	1 (4.8)	
Not appropriate (moribund)		1 (5)	1 (4.8)	
Energy target in ward (kcal/kg IBW*day)	*mean (SD)*	28.0 (2.1)	28.7 (3.8)	0.948
Energy intake (kcal/kg IBW*day)	*mean (SD)*	19.3 (4.7)	29.7 (6.1)	<0.001*
Adequacy to target (%)		68.6 (16.2)	104.2 (20.1)	<0.001*
Protein target in ward (g/kg*day)	*N (%)*			0.713
1,2 g/kg*day		2 (10)	3 (14.3)	
1,2-1,5 g/kg*day		5 (25)	7 (33.3)	
1,5 g/kg*day		13 (65)	11 (52.4)	
Protein intake (g/kg IBW*day)	*mean (SD)*	0.93 (0.21)	1.55 (0.22)	<0.001*
Adequacy to target (%)		65.0 (14.9)	109.9 (13.6)	<0.001*

IQR = Interquartile range; N = number; SD = Standard deviation; BMI = Body mass index; ICU = Intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; SAPS II = Simplified Acute Physiology Score; NUTRIC = Nutrition Risk in Critically ill; ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition; IBW = ideal bodyweight;

a) p-values were calculated using Chi Square test, Fisher Exact test, two sample T-test or Mann-Whitney U test where appropriate;

** p-value <0.05.*

Secondary outcomes

An overview of discharge destinations, in-hospital-, 3- and 6-month mortality rates, readmission to ICU and hospital, length of ICU and hospital stay, and differences in MRC and CPAx scores for low and high protein intake groups are summarized in **Table 7**.

No differences between groups were observed for any parameter (all p>0.05).

Table 7. Outcome parameters

			Overall protein adequacy		
		All patients (n=41)	<90% (n=20)	>90% (n=21)	p-value[a)]
Mortality	*N (%)*				
Hospital		2 (4.9)	1 (5)	1 (4.8)	0.972
3 months		6 (14.6)	4 (20)	2 (9.5)	0.410
6 months		7 (17.1)	5 (25)	2 (9.5)	0.238
Readmission to ICU (during hospital stay)	*N (%)*	3 (7.3)	1 (5)	2 (9.5)	0.578
Hospital readmission (yes)	*N (%)*	13 (31.7)	6 (30)	7 (33.3)	0.819
Within 3 months		8 (19.5)	4 (20)	4 (19.0)	
Within 6 months		10 (24.4)	6 (30)	4 (19.0)	
Within 12 months		13 (31.7)	6 (30)	7 (33.3)	
Composite endpoint mortality/HOS readmission[b)]	*N (%)*	16 (39.0)	10 (50)	6 (28.6)	0.097
Length of stay (days)	*median [IQR]*				
ICU		9 [5-22]	10 [5-12]	9 [6-27]	0.478
Hospital (after ICU discharge)		12 [8-15]	10 [7-14]	12 [8-15]	0.289
Discharged from hospital with FT/CVC (yes)	*N (%)*	11 (26.8)	0 (0)	11 (50)	0.002*
Discharge destination	*N (%)*				0.706
Home		18 (43.9)	10 (50)	8 (38.1)	
Revalidation		21 (51.2)	9 (45)	11 (52.4)	
Psychiatric unit		1 (2.4)	0 (0)	1 (4.8)	
Mortuary		2 (4.9)	1 (5)	1 (4.8)	
MRC score at ICU discharge	*median [IQR]*	45 [37-48]	47 [39-48]	42 [36-48]	0.402
MRC score at HOS discharge	*median [IQR]*	48 (46-5]	48 [48-52]	48 [45-50]	0.496
Difference MRC score (HOS - ICU discharge)	*median [IQR]*	3 [0-6]	2 [0-6]	4 [0-8]	0.264
CPAx score at ICU discharge	*median [IQR]*	33 [24-39]	35 [20-40]	32 [24-39]	0.282
CPAx score at HOS discharge	*median [IQR]*	42 [38-46]	42 [40-45]	42 [37-46]	0.830
Difference CPAx score (hospital - ICU discharge)	*median [IQR]*	7 [4-12]	7 [4-10]	7 [4-12]	0.977

N = number of patients; IQR = interquartile range; ICU = intensive care unit; HOS = hospital; FT = feeding tube; CVC = central venous catheter; MRC = Medical Research Council; CPAx = Chelsea Critical Care Physical Assessment tool;
a) p-values were calculated using Chi Square test, Fisher Exact test, two sample T-test or Mann-Whitney U test where appropriate;
b) composite endpoint composed of 6-month hospital readmission or 6-month mortality;
** p-value <0.05.*

The composite endpoint for unfavourable outcome (6-month hospital readmission or 6-month mortality) showed a positive trend for the high intake group, although this difference was not statistically significant (p=0.097). This trend disappeared in

univariable and multivariable COX regression with covariates gender, BMI and NUTRIC score (all p>0.05).

Discussion

The primary finding of this study is that energy and protein intake among post-ICU patients in general wards is below recommended and prescribed targets, due to insufficient (additional) oral intake. Mean overall energy and protein intake for all nutritional groups was 24.7 kcal/kg IBW*day and 1.25 g/kg IBW*day, corresponding to 82% and 83% of targets, respectively. Only 51.2% of patients reached >90% of prescribed protein targets during their post-ICU ward stay.

The observed adequacies are slightly higher than those reported in current literature. Chapple *et al.* reported energy and protein adequacies of 81% and 77% respectively, although their study population comprised 37 patients with moderate traumatic brain injury and not general ICU patients (17). Ridley *et al.* conducted a nested cohort study within a randomized controlled trial (RCT) comparing supplemental PN with standard care, studying nutritional intake of 32 patients in the post-ICU hospitalization period (15). They reported median overall energy and protein adequacies of 79% and 73%. Moisey *et al.* observed lower intakes, assessing nutritional intake in 19 patients during the first week after extubation (16). They found overall median adequacies of energy and protein intake of 71% and 46%, respectively. Wittholz *et al.* who studied nutritional intake of multi-trauma patients during the first 5 days after ICU discharge, reported adequacies of 64% and 72% for energy and protein intake, respectively (23). These reported adequacies might be lower than in our study because oral intake was the predominant nutritional mode during the study period (Ridley 55%, and Moisey 43% of study days versus 45% in our study). Moreover, differences in target calculations, assessment of nutritional intake (food record charts and patients recall) and days studied (second daily by Ridley *et al.,* and immediately after extubation up to 8 days by Moisey *et al.*) may have further contributed to these differences. All studies consistently demonstrate that protein and energy targets are not reached after ICU-discharge.

Importantly, adequacy was highly dependent on patients' nutritional route. Patients with oral nutrition only had the lowest intake as overall adequacies of 82.2% and 75.5% for energy and protein intake, were observed. Of note, these patients all received food fortification (energy/protein enriched) and/or ONS. In the aforementioned studies, patients only met up to 66% and 60% of prescribed energy and protein targets (15,16). When no oral supplements were provided, energy and protein adequacies were notably worse: 37% and 48%, respectively (15).

Two other studies investigating oral intake post-extubation support these findings and demonstrate that energy and protein intake are below prescribed targets in patients with oral nutrition only after EN discontinuation (18,24).

Clinicians should consider that the prescribed calories and proteins are neither ordered nor consumed. Even the amount of food ordered was inadequate compared to targets. In patients failing to meet protein prescriptions (adequacy <90%), we found that the amount of protein ordered was statistically significant less than prescribed (median 1.17 versus 1.33 g/kg IBW*day; p=0.018). In addition to this, prescriptions were below recommended protein intakse of at least 1.5g/kg*day (7-8). Similar findings were reported by Mitchell *et al.,* who demonstrated that neither prescriptions nor delivery of EN met targets in the post-ICU hospitalization period (25).

In contrast, the best energy and protein adequacies (≥95%) were observed among patients receiving (supplemental) (par)enteral nutrition until hospital discharge; none of these patients had an overall adequacy of <90% in our study. This is concordant with findings reported by Ridley *et al.,* who demonstrated adequacies of 104% and 99% for energy and protein targets, respectively, in patients receiving supplemental EN (15). However, not all of these EN patients reached their targets. Also, Chapple *et al.* reported energy and protein adequacies of 89% and 76% in patients receiving exclusive EN (17).

In most cases (81.3%), EN was terminated due to (supposed) sufficient energy and protein intake. However, 38.5% of these patients had an overall median protein adequacy of <90% before discontinuation. After EN discontinuation, the most significant drop in intake was seen during the first day. Subsequently, patients needed at least five days to reach a maximum adequacy at day 6 (median 75.2% and 103.2%, respectively), for energy and protein targets. After discontinuation of EN, the amounts of energy and proteins ordered by patients increased significantly, although this was still not enough to reach prescribed targets (median adequacy to energy and protein targets: 81.8% and 90.4%, respectively).

We noticed a sustaining second drop in intake at day 7 after cessation of EN to energy and protein adequacies of 70.5% and 79.1%, although few patients (n=7) were analyzed (as shown in **Supplement 6**). We hypothesize this is a result of discharge from the hospital of patients with the best adequacies (one patient with a protein adequacy of 111.7% in our study) or losing attention concerning adequate nutritional intake during the post-ICU hospitalization period.

Regarding secondary outcomes, no statistically significant clinical difference was found between patients reaching less or more than 90% of prescribed protein targets. This

lack of significance might be due to underpowerment as inclusions had to be stopped prematurely due to the COVID-19 pandemic. Weijs *et al.* studying 801 patients surviving the post-ICU hospitalization period, demonstrated a decrease in 90-day mortality rate after hospital discharge with 17% for each 1g/kg*day increase in protein intake (26). A multicenter trial by Schuetz *et al.* and multiple single-day audits of food intake during NutritionDay outside critical care emphasize these results. These studies demonstrated a better 30-day survival in patients with increased energy and protein intakes (19,27,28). We found no difference in global muscle strength (MRC score) between patients reaching 90% of protein targets or not, probably as this parameter has a ceiling effect, not being able to distinguish changes in patients with the highest scores.

Strengths

This study reports the most extensive and detailed observational data regarding meal consumption of post-ICU patients during their entire hospitalization period. We analyzed nearly 500 observational days using more than 1,600 pictures and over 6,500 meal order lines. Due to our hospital's meal order system, we were able to precisely quantify the number of kilocalories and grams of proteins ordered. All post-ICU hospitalization days were assessed until hospital discharge. Intake was measured daily (and before and after discontinuation of EN) in contrast with other studies (15-17). Furthermore, all data on in-between meals ordered were recorded, not available in other studies (17). Recall bias was eliminated as oral nutrition was objectively quantified through pre- and post-meal pictures, and assessed by two researchers independently after completing study participation (15,18). Inter-rater agreement was excellent (ICC 0.878), partly because 2,330 food order lines (35.1%) were graded 0 (not consumed), 1 (entirely consumed) or missing.

Limitations

Our study is limited by its single-center design and relatively small sample size. We aimed to include a larger sample, but inclusions had to be stopped prematurely due to the COVID-19 pandemic in March 2020. We might have introduced participants' bias among patients with oral nutrition. Patients were aware that their intake was measured daily. Moreover, the digital photography method has not been validated yet for non-trained observers. Only one study in a clinical setting has shown that the pre-post-meal picture method is valid and accurate compared with weighed food records in monitoring food intake in general wards (20). Additionally, the picture method is labour-intensive and has some disadvantages and limitations. Due to technical problems with the cameras, the nutritional assessment of five patients could not be performed. In 7 patients only a few days could be analyzed due to missing pictures or bad quality. Products such as jelly, sugar, soups and ONS were difficult to analyze due to their opaque packaging. Not

infrequently, packages from ordered products were missing in the post-meal photos, resulting in missing data which had to be extrapolated using less reliable methods.

We hypothesize that actual intake might be considerably lower than reported as details regarding food consumption by family members or thrown away before taking pictures was not considered. Moreover, due to poor registration, we could not collect data about gastric residual volumes and interruptions of (par)enteral nutrition in case of fasting for procedures or accidental feeding tube loss. This may contribute to nutritional shortfalls (17). Conversely, we were unable to retrieve food record charts that reported food not registered, such as food brought in by family members. Finally, nutritional intake is expressed as study population based averages or medians. Patients with the highest adequacies may conceal the real nutritional intakes of patients with the lowest intakes (**Supplement 4**).

Future directions

We recommend further studies to extend individualized nutritional support to reach energy and protein targets in the post-ICU period. In the EFFORT multicenter RCT, studying 2,088 general ward patients at risk for malnutrition, a beneficial effect of individualized nutritional support has been shown (19). Therefore, we suggest monitoring intake (from all nutritional routes) daily and only stop EN when oral intake has proven to be sufficient, as recommended by Ridley *et al.* (14). Subsequently, intake should be supported with food fortification or ONS, possibly even for a prolonged time after hospital discharge to facilitate recovery (10,12,14). When targets are not reached after cessation of EN, reintroduction of EN should be considered in selected cases. Moreover, the importance of ordering and consuming adequate amounts of energy including proteins should be emphasized.

Conclusion

Most patients recovering from critical illness did not reach energy and protein targets during the post-ICU hospitalization period. However, this was highly dependent on the nutritional route, and was lowest among patients with oral nutrition only (despite of food fortification strategies and/or ONS). Additionally, the ordered amount of food failed to meet the predicted targets. Conversely, the best intake was seen in patients with (supplemental) EN; all these patients reached adequacies >90%. Nonetheless, discontinuation of EN posed a nutritional risk, resulting in immediate and sustained drops of energy and protein intake. Patients needed an additional six days to increase intake to meet protein targets again. These findings highlight the need for follow-up studies to close the gap with individualized nutritional support in the post-ICU period. No statistically significant differences in clinical outcomes were observed in this study.

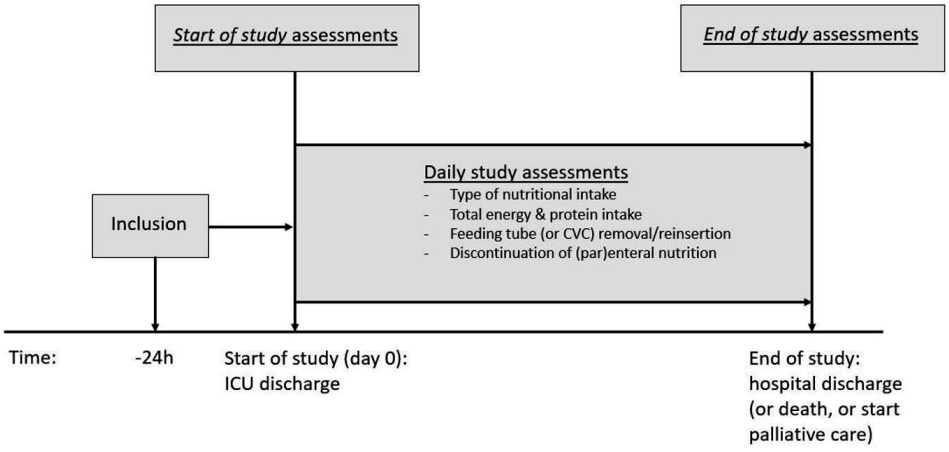
References

1. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019 Feb;38(1):48-79.
2. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009 Oct;35(10):1728-37.
3. Weijs PJ, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes AR, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr. 2012 Jan;36(1):60-8.
4. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211.
5. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured targets in intensive care patients. Clin Nutr. 2012 Aug;31(4):462-8.
6. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study. JPEN J Parenter Enteral Nutr. 2016 Jan;40(1):45-51.
7. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr. 2019 Feb;38(1):10-47.
8. Nutrition support for adults: oral nutrition support, enteral tube feeding, and parenteral nutrition. Guidance and guidelines. NICE [Internet]. Nice.org.uk. 2022 [cited 28 March 2022]. Available from: https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#screening-for-malnutrition-and-the-risk-of-malnutrition-in-hospital-and-the-community
9. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. Crit Care Med. 1999 Jul;27(7):1295-302.
10. Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. Crit Care. 2017 Dec 28;21(Suppl 3):316.
11. Obeid JN, Hodgson CL, Ridley EJ. Nutrition in the Post ICU Period: Where is the Evidence? ICU Manag & Pract. 2020;20(4):283-287.
12. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care. 2019 Nov 21;23(1):368.
13. Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW; Enhanced Recovery After Critical Illness Programme Group (ERACIP) investigators. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017 Aug 26;21(1):226.
14. Ridley EJ, Chapple LS, Chapman MJ. Nutrition intake in the post-ICU hospitalization period. Curr Opin Clin Nutr Metab Care. 2020 Mar;23(2):111-115.
15. Ridley EJ, Parke RL, Davies AR, Bailey M, Hodgson C, Deane AM, et al. What Happens to Nutrition Intake in the Post-Intensive care unit Hospitalization Period? An Observational Cohort Study in Critically Ill Adults. JPEN J Parenter Enteral Nutr. 2019 Jan;43(1):88-95.

16. Moisey LL, Pikul J, Keller H, Yeung CYE, Rahman A, Heyland DK, et al. Adequacy of Protein and Energy Intake in Critically Ill Adults Following Liberation From Mechanical Ventilation Is Dependent on Route of Nutrition Delivery. Nutr Clin Pract. 2021 Feb;36(1):201-212.
17. Chapple LS, Deane AM, Heyland DK, Lange K, Kranz AJ, Williams LT, et al. Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury. Clin Nutr. 2016 Dec;35(6):1315-1322.
18. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of oral intake in critically ill patients 1 week after extubation. J Am Diet Assoc. 2010 Mar;110(3):427-33.
19. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualized nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019 Jun 8;393(10188):2312-2321.
20. Winzer E, Luger M, Schindler K. Using digital photography in a clinical setting: a valid, accurate, and applicable method to assess food intake. Eur J Clin Nutr. 2018 Jun;72(6):879-887.
21. Doorduijn AS, van Gameren Y, Vasse E, de Roos NM. At Your Request(®) room service dining improves patient satisfaction, maintains nutritional status, and offers opportunities to improve intake. Clin Nutr. 2016 Oct;35(5):1174-80.
22. FAO/WHO/UNU Expert Consultation. Equations for the prediction of basal metabolic rate [internet]. Available from: http://www.fao.org/3/aa040e/AA040E15.htm [Accessed March 23, 2022].
23. Wittholz K, Fetterplace K, Clode M, George ES, MacIsaac CM, Judson R, et al. Measuring nutrition-related outcomes in a cohort of multi-trauma patients following intensive care unit discharge. J Hum Nutr Diet. 2020 Jun;33(3):414-422.
24. Jarden RJ, Sutton-Smith L, Boulton C. Oral intake evaluation in patients following critical illness: an ICU cohort study. Nurs Crit Care. 2018 Jul;23(4):179-185.
25. Mitchell A, Clemente R, Downer C, Greer F, Allan K, Collinson A, et al. Protein Provision in Critically Ill Adults Requiring Enteral Nutrition: Are Guidelines Being Met? Nutr Clin Pract. 2019 Feb;34(1):123-130.
26. Weijs PJM, Mogensen KM, Rawn JD, Christopher KB. Protein Intake, Nutritional Status and Outcomes in ICU Survivors: A Single Center Cohort Study. J Clin Med. 2019 Jan 4;8(1):43.
27. Hiesmayr M, Schindler K, Pernicka E, Schuh C, Schoeniger-Hekele A, Bauer P, et al; NutritionDay Audit Team. Decreased food intake is a risk factor for mortality in hospitalized patients: the NutritionDay survey 2006. Clin Nutr. 2009 Oct;28(5):484-91.
28. Sauer AC, Goates S, Malone A, Mogensen KM, Gewirtz G, Sulz I, et al. Prevalence of Malnutrition Risk and the Impact of Nutrition Risk on Hospital Outcomes: Results From nutritionDay in the US. JPEN J Parenter Enteral Nutr. 2019 Sep;43(7):918-926.

Supplemental material

Supplement 1. Study assessments



ICU = Intensive care unit; CVC = central venous catheter.

Supplement 2. Target calculations (energy / protein)

A) Energy targets

Male	
18-30y	15.4 x weight - 27 x length + 717
30-60y	11.3 x weight - 16 x length + 901
>60y	8.8 x weight + 1128 x length - 1071

Female	
18-30y	13.3 x weight + 334 x length + 35
30-60y	8.7 x weight - 25 x length + 865
>60y	9.2 x weight + 637 x length - 302

B) Protein targets

BMI ≤ 27	1.5 g/kg of actual body weight
BMI 27-30	1.5 g/kg, weight corrected to BMI 27
BMI 30-40	2.0 g/kg ideal body weight (male BMI 22.5; female BMI 21)
BMI ≥ 40	2.5 g/kg ideal body weight (male BMI 22.5; female BMI 21)

y = years; weight in kilograms; length in meters; BMI = Body mass index.

Supplement 3. Nutritional data – patients with oral nutrition only

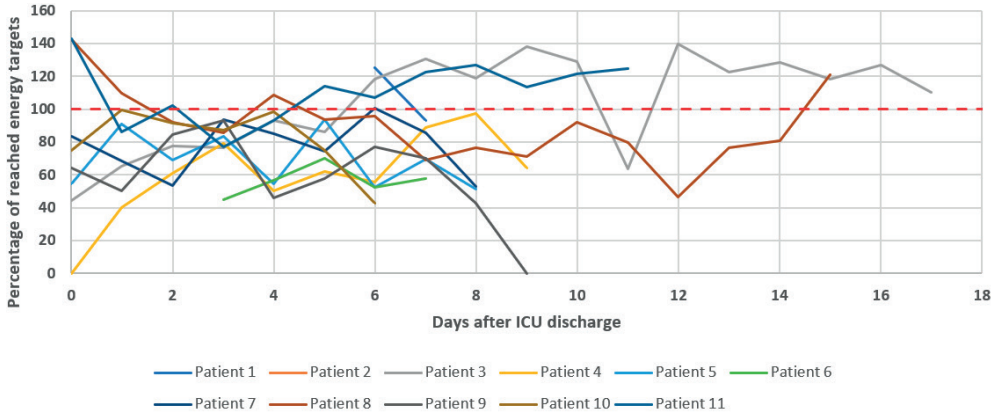
Patients with energy and/or protein adequacy <100%

		Target	Ordered	p-value[a)]	Intake	p-value[a)]	Adequacy (%)
Energy (kcal/kg IBW*day) (n=8)	*median [IQR]*	28.3 [26.4-30.6]	25.4 [24.4-26.6]	0.018*	20.4 [18.2-22.7]	0.018*	73.4 [65.2-84.2]
Protein (g/kg IBW*day) (n=9)	*median [IQR]*	1.41 [1.25-1.50]	1.22 [1.15-1.31]	0.012*	0.97 [0.86-1.18]	0.012*	76.8 [65.6-88.9]

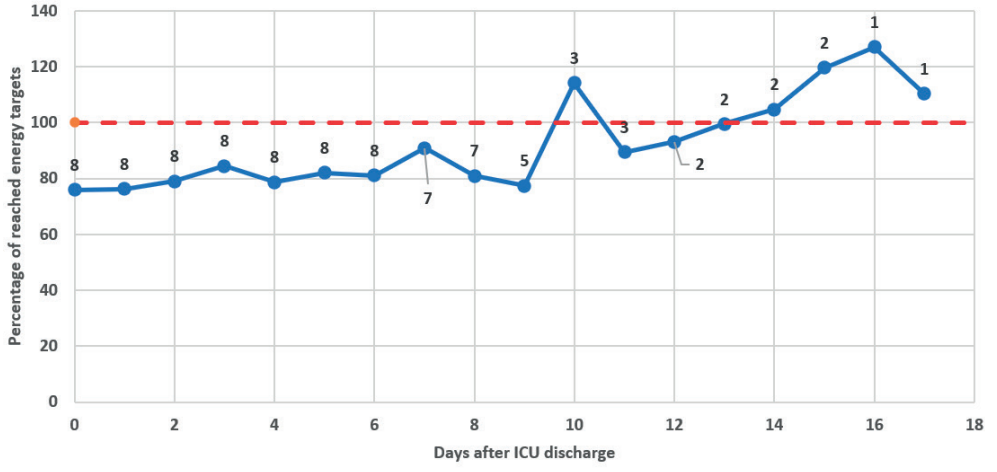
IBW = ideal bodyweight; IQR = Interquartile range;
*a) p-values were calculated using the one sample t-test and sign test where applicable (after calculating deficits in nutritional orders and intake compared to target); * p-value <0.05.*

Supplement 4. Visual representation of oral intake during the post-ICU hospitalization period

A) Adequacy of energy intake per day after ICU discharge (per patient)

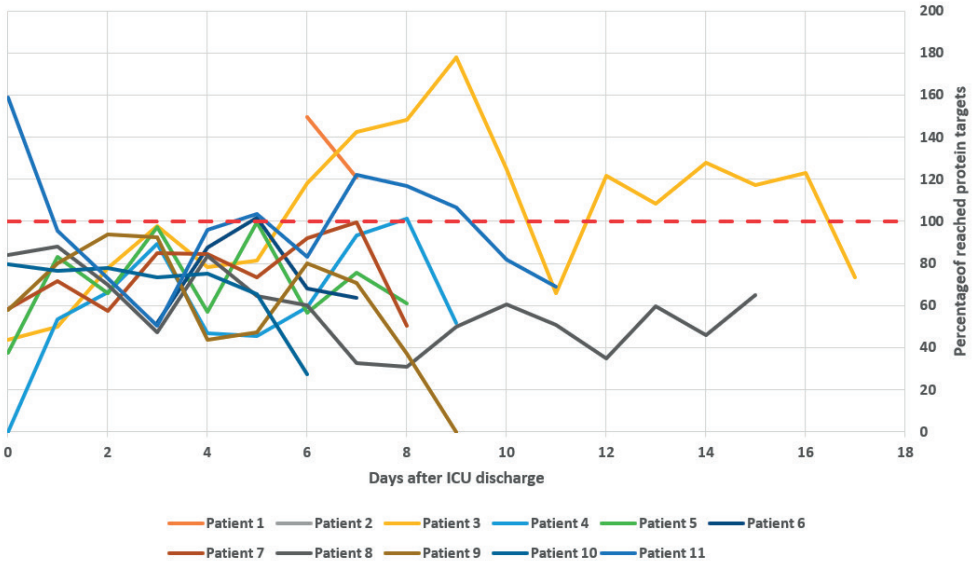


B) Mean adequacy of energy intake per day after ICU discharge (all patients averaged)

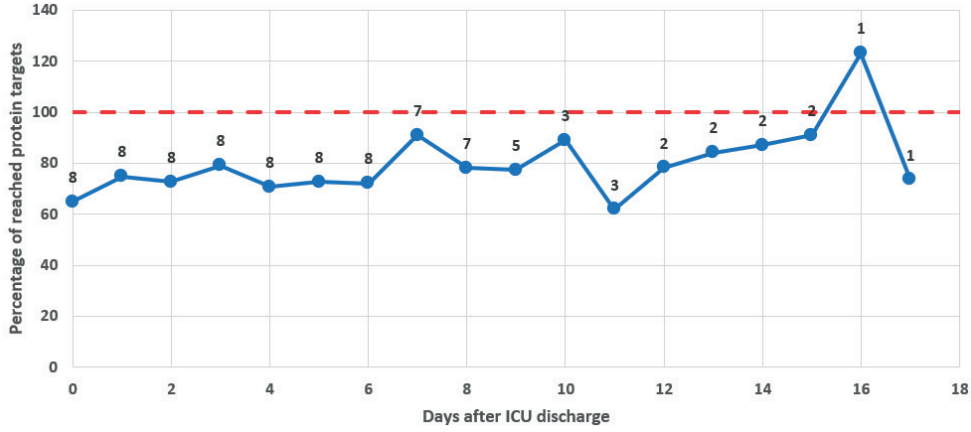


Numbers represent the number of observations.

C) Adequacy of protein intake per day after ICU discharge (per patient)



D) Mean adequacy of protein intake per day after ICU discharge (all patients averaged)



Numbers represent the number of observations.

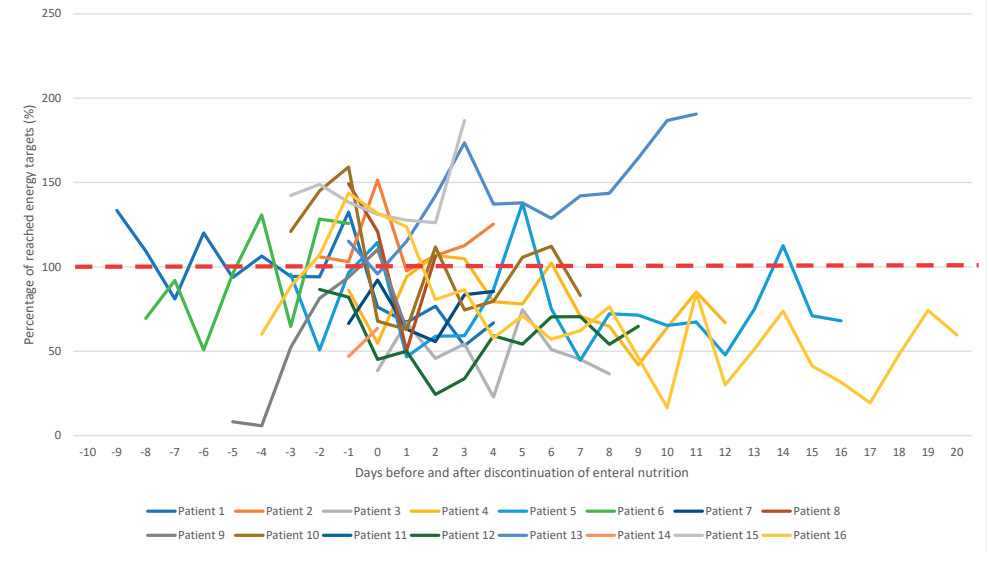
Supplement 5. Nutritional data - (par)enteral nutrition

		All patients	ORAL only[a)]	ORAL/ EN[a)]	EN only[a)]	PN ± EN ± ORAL[a)]	p-value[b)]
		(n=41)	(n= 11)	(n=14)	(n=13)	(n=3)	
Duration EN/PN in the ward before stop (days) (n=19)	*median [IQR]*	4 [2-6]	NA	3.5 [2-5]	5 [3-10]	2 & 5	0.266
FT/CVC at hospital discharge (yes)	*N (%)*						<0.001*
FT		10 (24.4)	0 (0)	4 (28.6)	6 (46.2)	0 (0.0)	
CVC		1 (2.4)	0 (0)	0 (0)	0 (0)	1 (33.3)	
Reason to stop EN/PN (n=18)	*N (%)*						<0.001*
Accidental removal FT/CVC		2 (10.5)	NA	1 (10)	1 (16.7)	0 (0)	
Sufficient intake		14 (73.7)	NA	8 (80)	5 (83.3)	1 (33.3)	
Patient refusal/complaints		1 (5.3)	NA	1 (10)	0 (0)	0 (0)	
Start palliative care		1 (5.3)	NA	0 (0)	0 (0)	1 (33.3)	

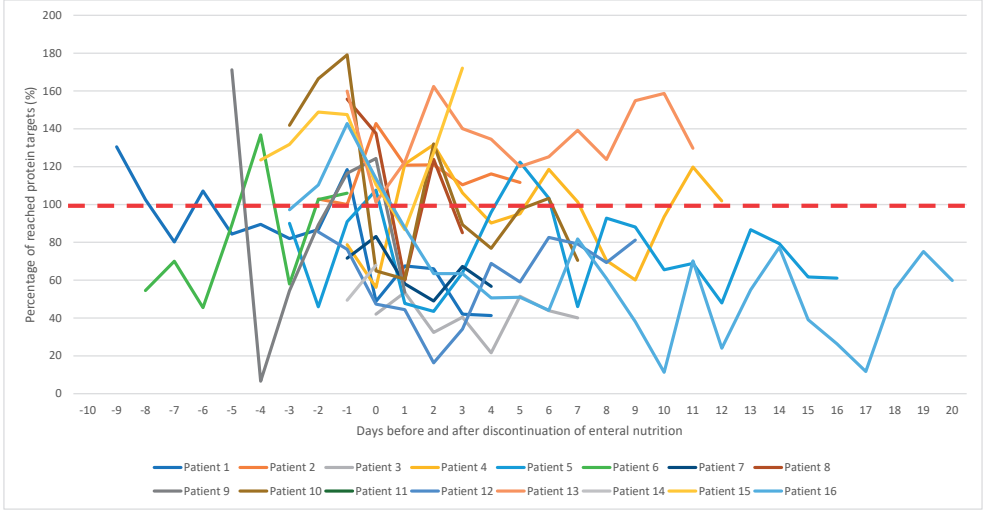
a) *Nutritional route at ICU discharge: ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition;*
b) *p-values were calculated using Fisher Exact or Kruskal Wallis test where appropriate;*
** p-value <0.05;*
IQR = Interquartile range; N = number; FT = feeding tube; CVC = central venous catheter.

Supplement 6. Discontinuation of enteral nutrition

A) Adequacy of energy intake before and after discontinuation of enteral nutrition (per patient)



B) Adequacy of protein intake before and after discontinuation of enteral nutrition (per patient)



Day 0 = discontinuation of enteral nutrition.

C) Patients with overall protein adequacy <100% before AND after stop EN (n=12)

		Before stop EN	After stop EN	p-value[a)]
Energy intake	*median [IQR]*			
Ordered (kcal/kg IBW*day)		13.5 [8.6-23.8]	21.2 [17.8-28.8]	0.018**
Intake (kcal/kg IBW*day)		24.7 [17.3-31.4]	19.1 [15.9-22.1]	0.398
Contribution EN (%)		52.7 [45.5-76.2]	NA	0.018**
Adequacy to target (%)		85.2 [61.9-100.6]	68.0 [59.7-78.0]	0.374
Protein intake	*median [IQR]*			
Ordered (g/kg IBW*day)		0.62 [0.35-1.05]	0.95 [0.93-1.61]	0.018**
Intake (g/kg IBW*day)		1.11 [0.91-1.67]	0.97 [0.74-1.14]	0.018**
Contribution EN (%)		60.7 [46.4-82.3]	NA	0.398
Adequacy to target (%)		81.9 [74.6-97.9]	62.8 [53.1-83.9]	0.173

Four patients with overall adequacies >100% before AND after discontinuation of EN were left out of this analysis;
[a)] Overall energy and protein intake before AND after discontinuation of EN were compared (including amounts of energy / proteins ordered, percentage of EN contributing and adequacy);
EN = Enteral Nutrition; IQR = Interquartile range; IBW = Ideal body weight.

D) Comparisons between observational days, patients with mean protein adequacy <100% before AND after stop EN (n=12)

		Day -1	Day 1	p-value[a)]	Day 3	p-value[a)]	Day 5	p-value[a)]	Day 7	p-value[a)]
		(n=8)	(n=8)		(n=8)		(n=6)		(n=6)	
Energy	*median [IQR]*	31.5 [21.8-39.3]	16.9 [14.4-23.1]	0.043*	18.2 [13.9-24.2]	0.043*	20.6 [17.9-30.3]	0.273	17.7 [12.9-19.3]	0.068
Adequacy		95.3 [78.2-135.3]	63.1 [49.2-73.9]	0.015*	59.2 [53.8-85.0]	0.063	76.3 [66.8-113.7]	0.225	66.4 [45.0-73.8]	0.043*
Protein	*median [IQR]*	1.56 [1.05-2.04]	0.84 [0.72-1.23]	0.043*	0.94 [0.61-1.13]	0.043*	1.02 [0.76-1.43]	0.273	0.96 [0.65-1.27]	0.144
Adequacy		98.5 [75.1-124.6]	58.1 [50.6-77.6]	0.036*	63.7 [40.8-83.8]	0.063	77.1 [51.4-103.7]	0.345	74.8 [44.5-86.7]	0.225

*Day 0 = stop EN; energy in kcal/kg IBW*day; protein in g/kg IBW*day; IQR = Interquartile range;*
Four patients with overall adequacies >100% before AND after discontinuation of EN were left out of this analysis;
Energy and protein intake before (day -1) AND during the subsequent days after discontinuation of EN were compared;
[a)] Observational days were compared to day -1 (=day before discontinuation of EN);
** p-value <0.05.*

E) Patients with reason to stop EN "sufficient intake" (n=13)

		Before stop EN	After stop EN	p-value[a)]
Energy intake	*median [IQR]*			
Ordered (kcal/kg IBW*day)		18.5 [13.2-25.5]	22.4 [19.0-31.6]	0.028*
Intake (kcal/kg IBW*day)		27.7 [16.4-36.9]	20.8 [17.8-30.5]	0.463
Contribution EN (%)		49.8 [44.2-55.2]	NA	0.028*
Adequacy to target (%)		99.8 [66.4-133.5]	77.0 [63.2-88.4]	0.575
Protein intake	*median [IQR]*			
Ordered (g/kg IBW*day)		0.83 [0.49-1.17]	1.16 [0.93-1.62]	0.028*
Intake (g/kg IBW*day)		1.45 [0.90-1.92]	1.10 [0.83-1.61]	0.249
Contribution EN (%)		49.8 [45.3-62.3]	NA	0.028*
Adequacy to target (%)		95.4 [78.8-155.7]	75.9 [53.6-100.6]	0.074

EN = enteral nutrition; IQR = Interquartile range; IBW = ideal bodyweight; NA = not applicable;
[a)] observational days were compared to day -1 (=day before discontinuation of EN);
** p-value <0.05.*

F) Comparisons between observational days, patients with reason to stop EN "sufficient intake" (n=13)

		Day -1	Day 1	p-value[a)]	Day 3	p-value[a)]	Day 5	p-value[a)]	Day 7	p-value[a)]
		(n=8)	(n=8)		(n=8)		(n=6)		(n=6)	
Energy	*median [IQR]*	35.6 [26.4-40.3]	17.4 [16.2-32.7]	0.068	21.7 [14.1-27.8]	0.180	20.7 [19.9-32.8]	0.180	18.7 [14.9-30.6]	0.180
Adequacy		125.7 [86.1-143.8]	66.9 [62.9-115.1]	0.013*	80.7 [56.9-122.1]	0.327	78.0 [72.8-121.8]	0.273	70.7 [53.7-112.6]	0.273
Protein	*median [IQR]*	1.76 [1.56-2.14]	1.00 [0.84-1.49]	0.068	1.01 [0.62-1.47]	0.109	1.28 [0.76-1.55]	0.180	1.22 [0.76-1.74]	0.180
Adequacy		118.5 [78.8-155.7]	64.1 [57.0-96.1]	0.021*	85.1 [52.8-123.2]	0.123	95.1 [51.3-108.8]	0.144	81.8 [55.3-120.3]	0.273

*Day 0 = stop EN; energy intake in kcal/kg IBW*day; protein intake in g/kg IBW*day; EN = enteral nutrition; IBW = ideal bodyweight;*
[a)] observational days were compared to day -1 (=day before discontinuation of EN); p-values were calculated using the Wilcoxon signed rank test;
** p-value <0.05.*

Supplement 7. Outcomes - stratified for nutritional routes

		All patients	ORAL only[a)]	ORAL/EN[a)]	EN only[a)]	PN ± EN ± ORAL[a)]	
		(n=41)	(n= 11)	(n=14)	(n=13)	(n=3)	p-value[b)]
Mortality	*N (%)*						
Hospital		2 (4.9)	0 (0)	0 (0)	1 (7.7)	1 (33.3)	<0.001*
3 months		6 (14.6)	2 (18.2)	1 (7.1)	2 (15.4)	1 (33.3)	0.140
6 months		7 (17.1)	2 (18.2)	1 (7.1)	3 (23.1)	1 (33.3)	0.160
Readmission to ICU (during hospital stay)	*N (%)*	3 (7.3)	1 (9.1)	0 (0)	1 (7.7)	1 (33.3)	0.158
Hospital readmission (yes)	*N (%)*	13 (31.7)	5 (45.5)	2 (14.3)	4 (30.8)	2 (66.7)	
Within 3 months		8 (19.5)	4 (36.4)	1 (7.1)	2 (15.4)	1 (33.3)	0.296
Within 6 months		10 (24.4)	5 (45.5)	2 (14.3)	2 (15.4)	1 (33.3)	0.285
Within 12 months		13 (31.7)	5 (45.5)	2 (14.3)	4 (30.8)	2 (66.7)	0.103
Length of stay (days)	*median [IQR]*						
ICU		9 [5-22]	5 [5-7]	10 [6-28]	18 [10-39]	7 [5-11]	0.027*
Hospital (after ICU discharge)		12 [8-15]	10 [9-15]	12 [8-12]	13 [8-18]	8 [7-17]	0.516
Discharged from hospital with FT/CVC (yes)	*N (%)*	11 (26.8)	NA	4 (28.6)	6 (46.2)	1 (33.3)	<0.001*
Discharge destination	*N (%)*						0.005*
Home		18 (43.9)	7 (63.6)	4 (28.6)	5 (38.5)	2 (66.7)	

Supplement 7. Continued

		All patients (n=41)	ORAL only[a] (n= 11)	ORAL/EN[a] (n=14)	EN only[a] (n=13)	PN ± EN ± ORAL[a] (n=3)	p-value[b]
Revalidation		21 (51.2)	4 (36.4)	9 (64.3)	8 (61.5)	0 (0)	
Psychiatric unit		1 (2.4)	0 (0)	1 (7.1)	0 (0)	0 (0)	
Mortuary		2 (4.9)	0 (0)	0 (0)	1 (7.7)	1 (33.3)	
Difference MRC score (hospital - ICU discharge)	*median [IQR]*	3 [0-6]	2 [0-6]	4 [2-6]	5 [1-10]	0 [0]	0.233
Difference CPAx score (hospital - ICU discharge)	*median [IQR]*	7 [4-12]	5 [2-7]	8 [5-12]	11 [5-24]	7 [no IQR]	0.137

[a] Nutritional route at ICU discharge: ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition;
[b] p-values were calculated using Chi Square test, Fisher Exact test, or Kruskal Wallis test where appropriate.
** p-value <0.05;*
N = number; IQR = Interquartile range; ICU = Intensive care unit; FT = feeding tube; CVC = central venous catheter; MRC = Medical Research Council; CPAx = Chelsea Critical Care Physical Assessment tool; NA = not applicable.

CHAPTER 7

Progression of peripheral blood mononuclear cell mitochondrial function during the early phase of sepsis in Intensive care unit patients: the MIC study

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Abstract

Background

Sepsis is a leading cause of ICU admission and is associated with high rates of multiorgan failure and mortality. Altered mitochondrial function is an essential component of the early sepsis syndrome. However, its progression over time in peripheral blood mononuclear cells (PBMCs), essential mediators of the initial inflammatory response, is thus far unclear. Our purpose is to investigate the progression of mitochondrial respiration in peripheral blood mononuclear cells (PBMCs) in the early phase of sepsis in ICU patients.

Methods

A single-centre prospective observational cohort study was conducted in sepsis patients and compared with age- and sex-matched controls. Patients with comorbidities known to affect mitochondrial function were excluded. We measured mitochondrial function using functional respirometry measurements (Oroboros O2K) in PBMCs thrice during the first week of ICU admission. Secondary endpoints included the associations between mitochondrial function and (I) sepsis severity and (II) clinical outcomes, including 3-month mortality.

Results

Basal and ATP-linked respiration and coupling efficiency were increased in sepsis patients (n=25) compared to matched controls (n=26) at all time points. No differences in maximal respiration (evoked by CCCP injection) were detected. Increased basal respiration was associated with 3-month mortality (HR 3.794, 95% CI 1.018-14.149, p=0.047). No differences were observed in other secondary outcomes.

Conclusion

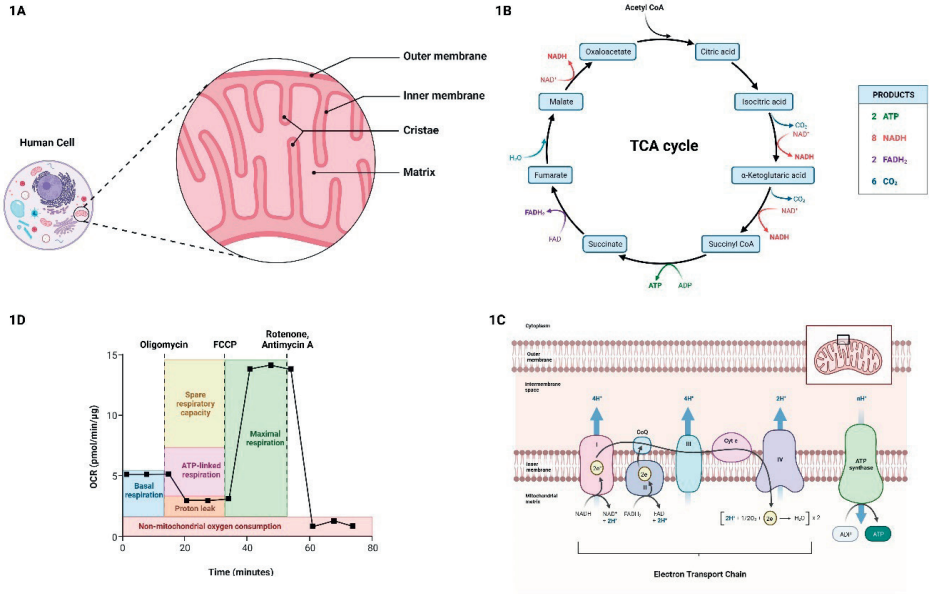
PBMC mitochondria were shown to have an increased respiratory rate during the first week of sepsis. Moreover, a progressive increase in mitochondrial respiration was negatively associated with 3-month survival.

Background

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, is a primary reason for admission to an Intensive care unit (ICU) [1]. Sepsis often contributes to (multi)organ failure and is associated with an average 30-day mortality of up to 35% of septic shock cases, accounting for about 20% of all global deaths in 2017 [2,3]. Sepsis survivors are at an increased risk of post-hospital discharge morbidity, mortality and a markedly reduced quality of life, which may last years after hospital discharge [4,5]. A lack of known therapeutic targets partly explains these poor clinical outcomes.

There is increasing evidence for the role of altered mitochondrial function in the pathogenesis of sepsis-associated multiple organ dysfunction syndrome [6-8]. The primary function of the mitochondria is to produce adenosine triphosphate (ATP), the universal energy donor in the cell. Mitochondrial respiration is the set of metabolic reactions and processes requiring oxygen at one of the final steps of the oxidative phosphorylation system (OXPHOS) in mitochondria to convert the energy stored in macronutrients to ATP [9-11] (**Figure 1**).

Figure 1. Title: Schematic overview of ATP production in a mitochondrion via the process of the citric acid cycle and oxidative phosphorylation



A. Mitochondria are organelles found in most human cells, the primary function of which is to generate energy in the form of adenosine triphosphate (ATP) through respiration;
B. The tricarboxylic acid cycle, also known as Krebs cycle, consumes acetate (in the form of acetyl-CoA) and water and reduces NAD+ to NADH, releasing carbon dioxide. The NADH generated by the citric acid cycle is fed into the oxidative phosphorylation (electron transport) pathway;
C. The electron transport chain (ETC) in the cell is the site of oxidative phosphorylation (OXPHOS). The NADH and succinate previously generated in the citric acid cycle are oxidized, releasing the energy of electron transport to power the ATP synthase;
D. Schematic of the contribution of the key parameters of OXPHOS to the mitochondrial oxygen consumption rate over time after addition of mitochondrial inhibitors;
Created with Biorender.com.

For example, pyruvate, derived from the breakdown of glucose, is converted into Acetyl-CoA which subsequently goes into the tricarboxylic acid (TCA) cycle to produce 2 ATP, 8 NADH and 2 $FADH_2$ molecules (**Figure 1B**). Both NADH and $FADH_2$ serve as crucial electron carriers for OXPHOS where electrons are ultimately donated to oxygen to form H_2O after being transported through four multiprotein complexes (**Figure 1C**). This results in a proton gradient across the inner mitochondrial membrane and the energy from this gradient is utilized by the FoF1 ATP-synthase to synthesize ATP. This process is called mitochondrial respiration and oxygen consumption can be used as a marker to assess the primary function of mitochondria **(Figure 1D**). A decreased mitochondrial respiration has been demonstrated in various cells in septic ICU patients, including muscle tissue and blood platelets [7-10,12-16]. However, in contrast to these results,

studies that measured mitochondrial function in peripheral blood mononuclear cells (PBMCs), which play an essential role in the initial (hyper)inflammatory response that hallmarks sepsis, have resulted in conflicting results.

Human peripheral blood mononuclear cells (PBMCs) are isolated from peripheral blood and identified as any blood cell with a round nucleus (i.e. lymphocytes, monocytes, natural killer cells and dendritic cells) [17]. Several studies reported a decreased mitochondrial function in PBMCs during sepsis [7,18], while others reported the opposite, namely an increased mitochondrial function [6,19]. One study even reported an increased mitochondrial respiration, but concomitantly, an increased mitochondrial uncoupling leading to reduced ATP-linked respiration [20]. Methodological differences, such as varying control groups and respiration mediums, might explain the inconsistency in the results of these studies. For example, the presence of plasma in the medium could influence the results, as suggested by the effects of incubating healthy cells in plasma of septic patients on mitochondrial respiration of PBMCs, as shown by Belikova and co-workers [6]. In addition, control groups were different, including, amongst others, critically ill postoperative patients [7] and non-septic patients with an infection [18].

Furthermore, in two of the mentioned studies, only one measurement was performed in each patient, which does not create insight into the progression of mitochondrial function in PBMCs during ICU stay [7,18]. This limitation is unfortunate since performing multiple measurements during ICU stay may reveal time-dependent effects of sepsis on mitochondrial function in PBMCs and its association with clinical outcomes. Although Sjövall *et al.* have performed multiple measurements during ICU stay, no correlations between the time-dependent changes in mitochondrial function during ICU stay and 3-month mortality were found [19]. On the contrary, Japiassú *et al.* reported a positive association between increased mitochondrial dysfunction and clinical outcomes, including organ failure and hospital mortality [7].

Rationale

We set out to fill several knowledge gaps based on previously reported studies. To be able to investigate whether mitochondrial derangements originate from the PBMCs themselves, we opted to resuspend the PBMCs in a standardized medium, not plasma. Secondly, studies assessing the potential time-dependent effects of sepsis on mitochondrial function in PBMCs are lacking. Therefore, we performed repeated mitochondrial respiration measurements during the first week of ICU stay. Lastly, we calculated correlations between clinical outcomes and mitochondrial function changes to reveal potential time-dependent associations between mitochondrial function and clinical outcomes.

Materials and methods

Study design and setting

A prospective, observational single-centre cohort study with an age- and sex-matched control group was conducted at Gelderse Vallei hospital (ZGV, Ede, The Netherlands) between January 1, 2018, and January 27, 2023. Due to the severe acute respiratory coronavirus 2 (SARS-CoV-2) pandemic, study inclusions were temporarily halted between March 14, 2020, and October 1, 2020. PBMC measurements were performed at Wageningen University and Research (WUR, Wageningen, The Netherlands).

Study participants

Patients (aged ≥18 years) admitted to the ICU with sepsis and/or septic shock were eligible for inclusion. Patients were enrolled after signing the informed consent by the patient or legal representative. According to the Third International Consensus Definitions, sepsis was defined as a new life-threatening organ dysfunction caused by a dysregulated host response to microbiologically confirmed or clinically suspected (supported by laboratory or radiology findings) infection, as identified by an increase in the sequential organ failure assessment (SOFA) score of ≥2 points. Septic shock was defined as the need for vasopressors to maintain a mean arterial pressure of ≥65 mmHg and serum lactate levels >2 mmol/L (>18 mg/dL) in the absence of hypovolaemia [1].

The control group was recruited from metabolically healthy short-stay hospitalised and outpatient clinic patients, individually matched for age and sex [21].

Patients from the sepsis and control groups were excluded from participation in the case of:

- Urosepsis [ICU patients only];
- Transfer from another ICU [ICU patients only];
- Serum haemoglobin level <5,5 mmol/L;
- Current hemodialysis or continuous renal replacement therapy;
- An expected survival of less than six months due to pre-existent underlying conditions (e.g., end-stage cancer);
- Treatment with chemo-, immune- and/or radiotherapy within the past 12 months;
- A significant event leading to hospitalisation within the previous six months;
- History of solid organ or bone marrow transplant;
- History of drug abuse;
- Family history of mitochondrial disease(s);
- Treatment with any investigational agent in the previous 12 months;

- Treatment with *systemic* corticosteroids or other immunosuppressive medications for active autoimmune disease involving the lung, heart, liver, small or large intestine, or neuromuscular system within three months prior to ICU admission;
- Pregnancy;
- Diabetes Mellitus type I or II [pre-ICU-admission where applicable];
- COPD GOLD stage III or IV or other severe respiratory disorders (FEV1 <30% and FEV1/FVC < 0.7) [pre-ICU admission where applicable];
- Any stage of acute or chronic renal failure [pre-ICU admission, where applicable];
- Any stage of acute or chronic liver failure [pre-ICU admission, where applicable];
- Consumption of >25 grams of ethanol daily (>2.5 alcoholic beverages/day);
- Not able to understand the Dutch language;
- Current participation in intervention research.

Study objectives

The primary study objective was to investigate the progression of mitochondrial respiratory function in PBMCs in septic ICU patients during the first week of ICU admission. Secondary objectives were to investigate the association between mitochondrial respiratory function and (I) sepsis severity and (II) clinical outcomes, including ICU-, hospital and 3-month mortality, length of ICU and hospital stay (LOS) and duration of mechanical ventilation.

Data collection

This study used PBMCs to measure mitochondrial respiratory function.

Sepsis group

Arterial blood samples were collected at three time points via an indwelling arterial access: day 1-2 (24-48h), day 3-4 (72-96h) and day 5-6 (120-144h) after ICU admission (indicated with T1, T2 and T3), respectively. A maximum of 70 mL of whole blood was collected per time point.

Control group

The control group underwent blood sampling by venepuncture with a vacutainer once during their visit to the outpatient clinic or short-stay hospitalisation. No physical tests were performed in this group.

PBMC isolation, washing and counting

Blood samples for PBMC isolation were collected in sodium citrate buffered cell preparation tubes containing a ficoll solution and centrifuged at 1000g for 30 minutes at room temperature. Next, PBMCs were resuspended in warm (37°C) 10mL of Hank Balanced Salt Solution and centrifuged at 400g for 10 minutes at room temperature.

The supernatant was then removed, and this washing step was repeated twice. After washing, the resulting PBMC pellet was resuspended in 1 mL of warm (37°C) Seahorse XF base medium supplemented with 2 mM glutamine and 25 mM glucose. The PBMCs were counted using the Cellometer auto T4, and cell viability was assessed by mixing 10 µL of cells with 10 µL acridine orange and propidium iodide stain. PBMCs were then immediately used for high-resolution respirometry.

High-resolution respirometry

Two to five million live PBMCs were injected into a chamber of the Oroboros O2K (Oxygraph-2k Oroboros Instruments, Innsbruck, Austria). The chamber volume was set to 2mL and filled with Agilent Seahorse XF Base medium supplemented with 25 mM glucose and two mM glutamate, and the pH was set to 7.4. The temperature within the chamber was set to 37°C, stirring speed to 750 rotations per minute. Oxygen concentration is continuously measured, recorded and used to calculate oxygen flux per one million live PBMCs using DatLab Software 4.3 (Oroboros Instruments, Innsbruck, Austria) (**Figure 1**).

After injection of the PBMCs, the basal respiration was recorded first. Second, oligomycin (2.5 µM) was added, which induced a state in which respiration is primarily to compensate for proton leakage. Third, carbonyl cyanide m-chlorophenylhydrazone (CCCP) was added repeatedly (20 nM) until maximum mitochondrial respiration was reached. Fourth, the complex I inhibitor rotenone and the complex III inhibitor, antimycin A, were added (0.5 µM and 2.5 µM, respectively) to determine non-mitochondrial respiration. Each step of the function profiling test was recorded after respiration had stabilised. Additionally, three parameters were calculated. ATP-linked respiration was calculated by subtracting leak respiration from basal respiration. Coupling efficiency was calculated by dividing ATP-linked respiration by basal respiration. Spare respiratory capacity was calculated by subtracting basal respiration from the maximal respiration.

Additional data sources

Data collection from the electronic medical record systems MetaVision® (iMDsoft, Tel Aviv, Israel) and NeoZIS® (MI Consultancy, Katwijk, The Netherlands) included baseline patient characteristics (including disease severity scores), laboratory values and outcome parameters, such as duration of mechanical ventilation and length of ICU and hospital stay.

Study size

Japiassú *et al.* previously studied maximal mitochondrial oxygen consumption in PBMCs of septic ICU patients (n = 20) and critically ill postoperative patients (n = 18) [7]. Oxygen consumption was significantly reduced in the septic ICU patient group compared to

the control group (5.60 ± 2.0 nmol O_2/min/10^7 cells versus 9.89 ± 3.8 nmol O_2/min/10^7 cells, respectively, $p<0.01$). Assuming altered mitochondrial function (measured as mitochondrial oxygen consumption) during sepsis develops linearly, the expected difference (effect size) between the measurements at the three different time points is similar to 50% of the observed differences by Japiassú et al. Therefore, to achieve a power of 0.95 with a two-sided significance level of 0.05, 30 subjects per group were needed (as calculated with G*power, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

When three valid measurements from an ICU subject could not be obtained due to withdrawal of consent, death, early ICU discharge or technical problems, patients were not matched with a control subject. Moreover, additional patients were included consecutively until complete measurements were obtained in 30 patients. Separate measurements from patients who did not have three complete consecutive measurements were included in the first analyses. The Cox regression models and ANOVA analyses also included patients with valid measurements at T1 and T3.

Statistical analyses

Data verification was conducted manually. Descriptive statistics were performed for demographic and clinical data of all patients and the primary outcome. Normality was assessed numerically and graphically. Continuous values were reported as means with standard deviations (SD; parametric data) or medians with interquartile ranges [IQR; non-parametric data]. Discrete data were presented as proportions (%). Differences in baseline characteristics and clinical outcomes between the sepsis and control group were assessed using the independent samples t-test, Wilcoxon rank sum, Wilcoxon signed rank, chi-squared, or Fisher's exact tests where appropriate.

Secondary outcomes were evaluated using uni- and multivariable Cox proportional hazards regression models or ANOVA analyses where appropriate. Multivariable Cox regression analyses were performed using the Enter and Forward Stepwise Wald methods.

Based on literature and clinical relevance, the variables age, sex, body mass index (BMI), acute physiology and chronic health evaluation II (APACHE II), SOFA and modified nutrition risk in critically ill (mNUTRIC) scores were analyzed in regression analyses. Variables were dichotomised (using the median) in case of non-linearity, with the outcome parameter assessed by visual inspection of boxplots.

Finally, all samples' PBMC lymphocyte-monocyte ratios (LMR) were calculated. Their changes over time and differences between survivors and non-survivors were evaluated. Moreover, correlation with parameters of mitochondrial function was assessed using Kendall's Tau-b.

Multicollinearity was assessed using the variance inflation factor (VIF); a value below two was considered acceptable.

IBM SPSS statistics 27 (I.B.M. Corp, Armonk, NY, USA) was used for all analyses and figures representing statistics. Only two-sided analyses were used. P-values ≤0.05 were considered statistically significant.

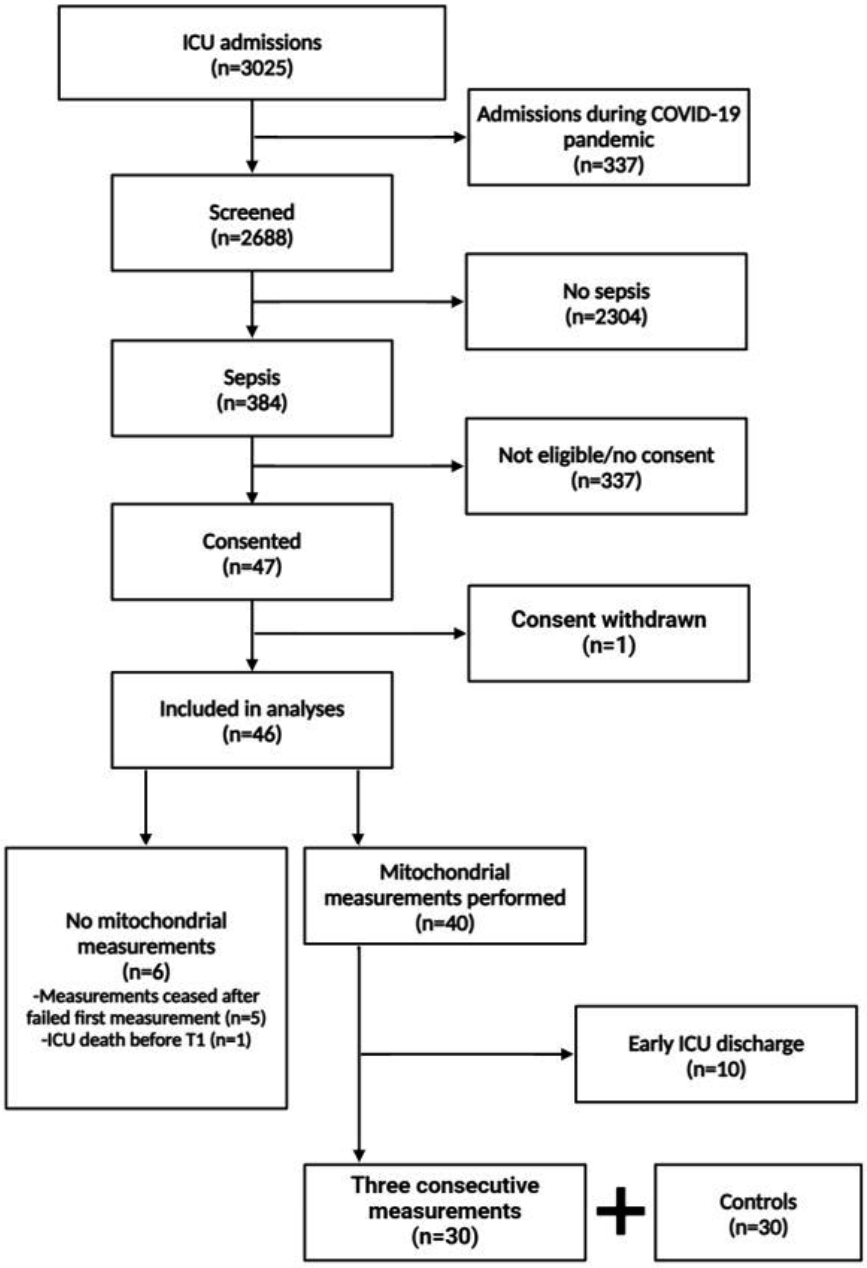
Ethical approval

The study was approved by the Medical Ethical Committee of Wageningen University (METC-WUR, which was incorporated in the METC Oost-Nederland in 2021, dossier no. 2021-13011) and the assessment Committee for Scientific Research of ZGV (dossier no. 1801-004). The protocol was registered in the Netherlands Trial Register (number NTR6969) and was made available through the International Clinical Trial Registry Platform (NL5918).

Results

Informed consent was obtained from 47 septic patients and 30 age- and sex-matched controls (**Figure 2**). One sepsis patient was excluded from analyses and further measurements after the withdrawal of consent.

Figure 2. Study flowchart



ICU = Intensive care unit. Created with Biorender.com.

The septic patients were predominantly male (n=33, 72%) and had a mean age of 68 (SD 13) years of age, with a mean BMI of 27 (SD 6) kg/m^2. The primary type of sepsis was pneumosepsis (n=24, 52%), followed by abdominal sepsis (n=17, 37%). At baseline, patients had the following clinical scores: mNUTRIC 5 [IQR 3-6], SOFA 8 [7-10] and APACHE II 18 [14-22]. The control patients were matched and subsequently predominantly male as well (n=22, 73%) and had a mean age of 71 (SD 15) years, which was not different from the sepsis group (p=0.3).

Study measurements

Six patients were excluded from further study participation due to death (one patient) or failure of the first measurement (five patients). Mitochondrial respiration data were collected from 40 patients, of whom ten patients were discharged to the general ward before the second (T2, n=3) or third (T3, n=7) measurement could be performed. The other 30 patients completed the measurements at all three consecutive time points for which age (± 2 years) and sex-matched controls were sought. When reviewing the obtained data after study completion, single respirometry measurements in five patients were discarded as they did not meet quality standards (T1 n=1, T2 n=1, T3 n=2 and T1-3 n=1). Measurements failed in four controls (13 %) and partially failed (no reaction to CCCP, rendering basal respiration and proton leak useable) in one patient.

The clinical patient characteristics at the time of blood samplings are shown in **Table 1**.

Table 1. Patient and control characteristics at time of the blood samplings

	Controls (n=26)	Sepsis patients (n=40[a])								
		T1 (n=38)		p-value[b]	T2 (n=35)		p-value[c]	T3 (n=28)		p-value[d]
SOFA score	NA	6 [4-8]		NA	4 [3-8]		<0.001*	5 [3-7]		<0.001*
Lactate (mmol/L)	NA	1.2 [0.8-1.7]		NA	0.9 [0.8-1.2]		0.002*	0.8 [0.6-1.2]		<0.001*
Leukocytes (*10^9/L)	6.5 [5.7 – 8.0]	13.6 [10.0-18.9]		<0.001*	12.7 [9.1-16.3]		0.189	12.2 [9.4-19.1]		0.388
PBMC LMR	4.6 [3.3-5.6]	2.0 [1.1-3.0]		0.010*	2.0 [1.5-3.3]		0.465	2.0 [1.3-3.0]		0.670
CRP (mg/L)	0	249 [148-323]		<0.001*	120 [77-214]		<0.001*	109 [58-204]		<0.001*
Ureum (mmol/L)	6.3 [5.5 – 7.1]	10.7 [7.8-19.5]	n=26	0.002*	11 [5.5-25]	n=20	0.844	10.1 [7.5-15.8]	n=18	0.529
Creatinine (umol/L)	74 [62 – 87]	84 [60-145]		0.024*	72 [52-117]		0.002*	60 [46-112]		<0.001*
Cortisol (nmol/L)	395 [311 – 472]	724 [546-1568]		<0.001*	676 [418-1005]		<0.01*	592 [431-725]		<0.001*
Insulin (mmol/L)	19 [9.4 – 18.5]	18 [8.8-30]		0.280	21 [12-35]		0.523	11.5 [7.7-31.5]		0.755
Insulin supplementation (IU)	NA	0 [0-19]		NA	0 [0-24]		0.449	0 [0-26]		0.234

[a] Unless stated otherwise due to missing variables;
[b] T1 compared to the control group; p-values were calculated using the Wilcoxon signed rank test;
[c] T1 compared to T2, p-values were calculated using the Wilcoxon signed rank test;
[d] T1 compared to T3, p-values were calculated using the Wilcoxon signed rank test;
** p-value <0.05;*
T1 = day 1-2 (24-48h); T2 = day 3-4 (72-96h); T3 = day 5-6 (120-144h) after ICU admission; SOFA = Sequential Organ Failure Assessment; NA = not applicable; PBMC = peripheral blood mononuclear cell; LMR = lymphocyte-monocyte ratio; CRP = C-reactive protein; IU = international units;
All values are reported as medians with interquartile ranges.

Mitochondrial function over time in septic patients and controls

Basal respiration and ATP-linked respiration were significantly increased in patients with sepsis compared to controls within the first week of ICU admission (median 4.27 [IQR 2.70-6.07] versus 2.24 [1.67-3.58] and 2.84 [1.32-4.04] versus 1.37 [0.75-2.02], respectively), as shown in **Figure 3** (and **Supplement 1**). No significant change in any other respiratory parameter was observed over time in the PBMCs of the entire sepsis group, as depicted in measurements T2 and T3 (all paired comparisons with T1 $p>0.05$).

Survivors versus non-survivors

All-cause 3-month mortality in the sepsis cohort (n=40) was 35% (n=14). Five (36%) of the deceased patients died in the ICU, seven (50%) in the ward and two after hospital discharge (14%). Compared to the surviving patients (n=31), the non-survivors (n=15) were older (77 (SD 10) versus 63 (SD 13) years of age, $p<0.001$), had higher APACHE II (median 20 [IQR 17-26] versus 15 [12-20], $p=0.008$] and mNUTRIC scores (6 [IQR 6-7] versus 4 [3-5], $p<0.001$) at ICU admission. No significant differences were found in other baseline characteristics.

Regarding biochemical parameters, survivors (results obtained for n=26) had higher serum insulin levels (20.0 [IQR 11.4-36.3] versus 8.4 [4.6-20.5], $p=0.014$) than non-survivors (results obtained for n=12) at T1, although they tended to have less insulin supplementation ($p=0.066$). No statistically significant differences in other laboratory parameters were found (**Table 2**).

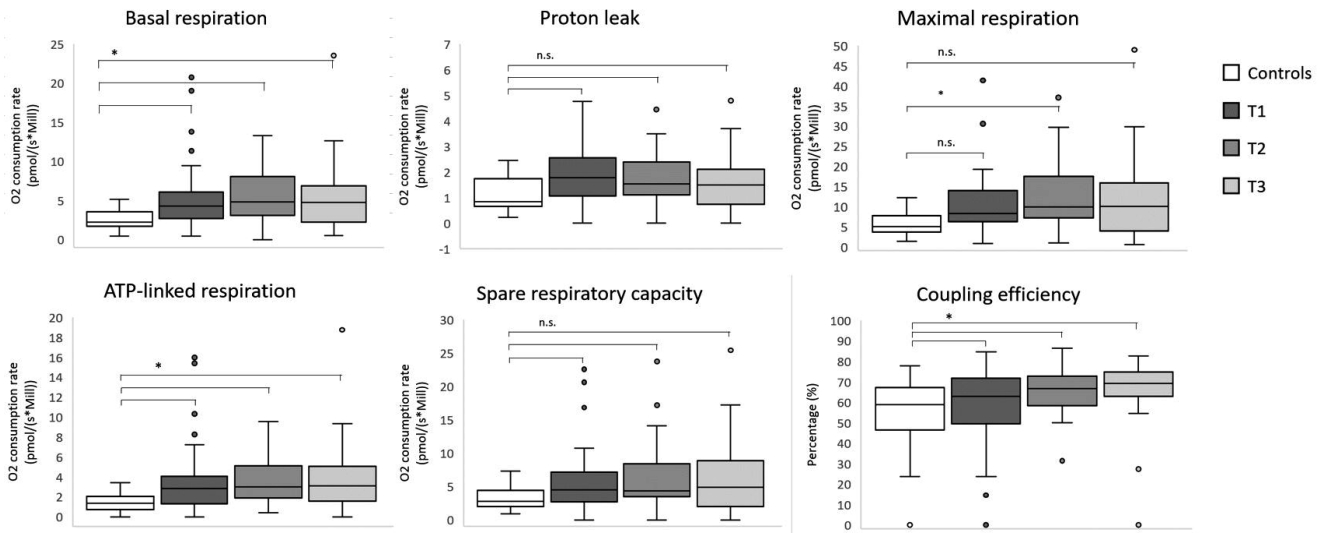
In high-resolution respirometry, mitochondrial proton leak was significantly lower in non-survivors compared to survivors (1.14 [IQR 0.86-1.97] versus 2.04 [IQR 1.28-2.90] nmol O_2/min/10^7, $p=0.048$) at T1. Moreover, a significant increase in basal and ATP-linked respiration was observed over time in non-survivors compared to survivors, as shown in **Figures 4** and **5 (Supplements 2 and 3)**.

Table 2. Survivors (n=26)[a] versus all-cause 3-month non-survivors (n=14)[a)]

	T1			T2			T3		
	survivors (n=26)	**non-survivors (n=12)**	**p-value**	**survivors (n=22)**	**non-survivors (n=13)**	**p-value**	**survivors (n=15)**	**non-survivors (n=13)**	**p-value**
SOFA score	6 [3-8]	7 [5-8]	0.6	3 [2-7]	5 [4-6]	0.3	4 [2-8]	5 [3-5]	0.9
Lactate (mmol/L)	1.3 [0.8-1.725]	1.2 [1.0-1.6]	0.9	0.9 [0.8-1.3]	1.0 [0.7-1.3]	0.9	0.8 [0.5-1.2]	0.9 [0.7-1.2]	0.5
Leukocytes (*10^9/L)	14.3 [8.5-19.0]	12.8 [10.5-16.8]	1.0	12.5 [9.1-16.3]	13.2 [8.2-16.6]	1.0	12.1 [9.5-17.7]	14.9 [9.2-22.6]	0.3
PBMC LMR	2 [1.1-3.1]	1.6 [1.0-3.9] n=9	1.0	2.3 [1.5-3.6] n=21	1.8 [1.2-2.4]	0.3	2.0 [1.7-3.5]	2.0 [1.1-2.5]	0.2
CRP (mg/L)	252 [169-323]	236 [137-318]	0.63	140 [74-214]	112 [87-280]	0.9	109 [70-168]	97 [35-212]	0.8
Ureum (mmol/L)	10.3 [6.5-18.2]	11.4 [9.1-25.2]	0.3	10.8 [5.1-14.4]	16.4 [8.8-32.6]	0.3	10.8 [6.6-24.7]	9.4 [7.9-14.4]	0.5
Creatinine (umol/L)	84 [57-188]	95 [75-132]	0.9	70 [52-114]	66 [52-124]	0.7	64 [46-137]	53 [44-109]	0.4
Cortisol (nmol/L)	674 [560-1397]	1398 [525-1959]	0.2	549 [418-1005]	697 [583-1062]	0.5	617 [368-761]	601 [506-768]	0.6
Insulin (mmol/L)	20.0 [11.4-36.3]	8.4 [4.6-20.5]	0.014*	20 [12-35]	17.5 [7.9-40.3]	0.8	12.5 [9.1-25.8]	13.0 [5.7-35.8]	1.0
Insulin supplementation (IU)	0 [0-0.75]	9 [0-38]	0.066	0 [0-1]	0 [0-45]	0.3	0 [0-0.75]	0 [0-31]	0.3
Insulin supplementation (IU)[b)]	32 [5-55]	36 [28-54]	0.5	41 [8-95]	45 [38-87]	0.6	50 [13-59]	36 [21-57]	0.8

[a] Unless stated otherwise due to missing variables;
[b)] only patients with insulin supplementation included;
** p-value <0.05;*
T1 = day 1-2 (24-48h); T2 = day 3-4 (72-96h); T3 = day 5-6 (120-144h) after ICU admission;
SOFA = Sequential Organ Failure Assessment; NA = not applicable; PBMC = peripheral blood mononuclear cell; LMR = lymphocyte-monocyte ratio; CRP = C-reactive protein; IU = international units;
All values are reported as medians with interquartile ranges. P-values were calculated using the Mann-Whitney U test.

Figure 3. Progression of mitochondrial respiratory parameters during the first week of ICU admission in septic patients and controls



*T1 = day 1-2 (24-48h); T2 = day 3-4 (72-96h); T3 = day 5-6 (120-144h) after ICU admission; n.s. = not statistically significant different; * = p-value <0.05.*

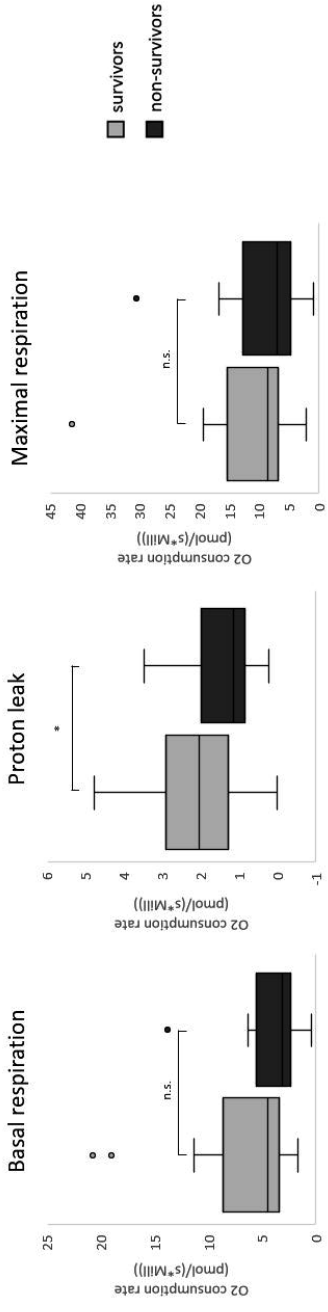
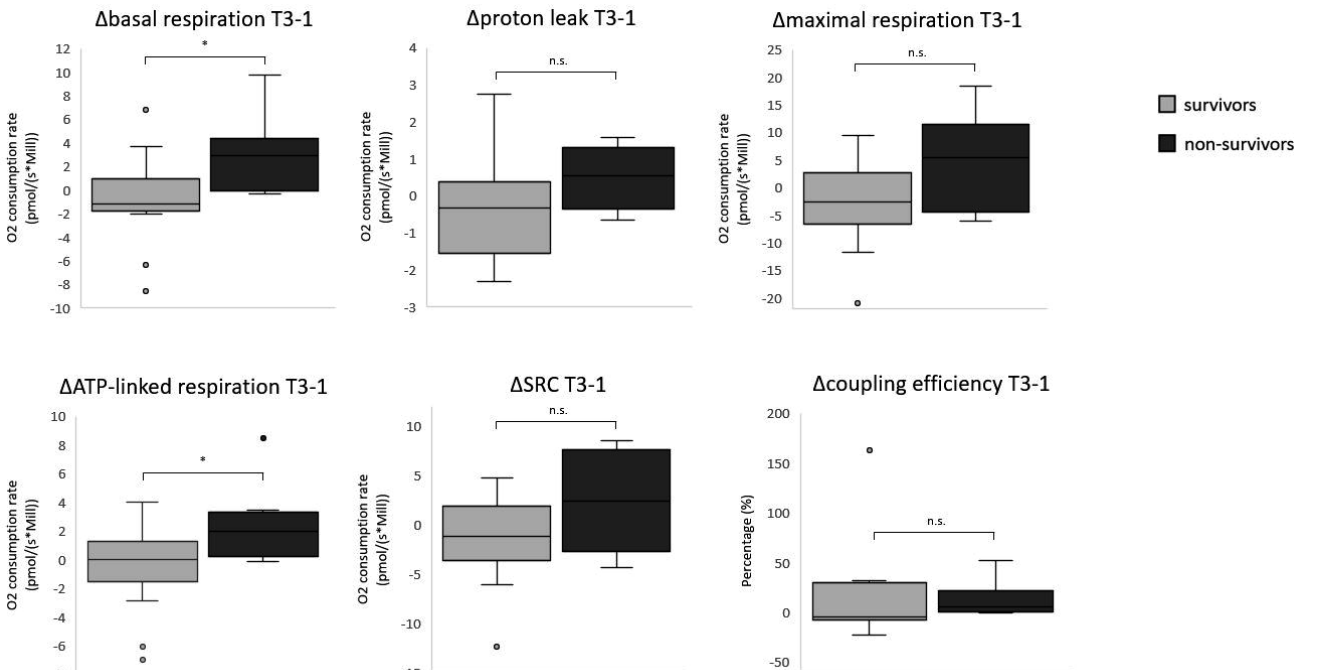


Figure 4. Comparison of mitochondrial respiratory parameters at T1 of sepsis survivors versus non-survivors

*T1 = day 1-2 (24-48h) after ICU admission; n.s. = not statistically significant different; * = p-value <0.05.*

Figure 5. Comparison of the progression of mitochondrial respiratory parameters during the first week of ICU stay of sepsis survivors and non-survivors



*Δ = delta (as measured T3 minus T1); SRC = spare respiratory capacity; T1 = day 1-2 (24-48h); T3 = day 5-6 (120-144h) after ICU admission; n.s. = not statistically significant different; * = p-value <0.05.*

Cox regression

The variables age and mNUTRIC were omitted in the final regression models because of their overlap (and visual correlation) with the APACHE II score. Measured mitochondrial respiration parameters were intercorrelated (all $p<0.01$); therefore, only basal respiration was used in the final model. None of the mitochondrial respiratory parameters were correlated with the SOFA score. The deltas of these two parameters over time were entered into the final model (ΔSOFA and Δbasal respiration as calculated by T3 minus T1). In the final Cox regression multivariable model, Δbasal respiration (≥0.07 nmol O_2/min/10^7 from T1 to T3) was associated with the primary endpoint of 3-month mortality (HR 3.8, 95% CI 1.0-14.1, p=0.047) (see **Table 3**). The VIF was <2 for the variables in this final model.

Other secondary outcomes

Only two patients needed a tracheostomy to wean from mechanical ventilation. An overview of the duration of mechanical ventilation and ICU and hospital LOS for survivors and non-survivors is summarized in **Supplement 4**. There were no statistically significant differences between both subgroups in these outcomes. In addition, delta basal respiration was not associated with the secondary outcomes, as shown in **Supplement 5**.

Lymphocyte-monocyte ratio

The PBMC LMR was lower in sepsis patients than in controls. No change over time (T1-T3) was noted, nor were any differences between survivors and non-survivors (**Tables 1-2**). Moreover, parameters of mitochondrial function did not correlate with the LMR, except LMR and proton leak on T3 (CC -0.267, p=0.05) (**Supplement 5**).

Table 3. Univariable and multivariable COX regressions for the association of primary endpoint 3-month mortality, baseline and clinical characteristics and mitochondrial respiratory function (n=40).

	Univariable	p-value	Multivariable	p-value
	HR (95% CI)		HR (95% CI)	
A. 3-month mortality (n=14)				
Sex (female)	1.060 (0.332-3.385)	0.9	0.707 (0.164-3.051)	0.6
BMI (>25.7)	1.040 (0.364-2.967)	0.9	1.400 (0.381-5.139)	0.6
APACHE II on admission (>18)	2.029 (0.703-5.859)	0.2	1.926 (0.509-7.289)	0.3
delta SOFA T3-1 (≥-2)	0.863 (0.303-2.463)	0.8	1.038 (0.218-3.832)	0.9
delta basal T3-1 (>0.068**)	3.041 (0.886-10.431)	0.08	3.794 (1.018-14.149)	0.047*
B. ICU mortality (n=5)				
Sex (female)	1.633 (0.182-14.639)	0.7	Difficulties with multivariable regression due to low number of deaths	
BMI (>25.7)	1.578 (0.263-9.460)	0.6		
APACHE II on admission (>18)	2.139 (0.356-12.861)	0.4		
delta SOFA T3-1 (≥-2)**	0.223 (0.025-1.998)	0.2		
delta basal T3-1 (>0.068**)	118 (0.007-2.121*10^6)	0.3		
C. Hospital mortality (n=7)				
Sex (female)	1.291 (0.349-4.775)	0.7	0.979 (0.183-5.228)	0.9
BMI (>25.7)	1.028 (0.331-3.192)	1.0	1.554 (0.389-6.207)	0.5
APACHE II on admission (>18)	1.490 (0.480-4.630)	0.5	1.232 (0.288-5.273)	0.8
delta SOFA T3-1 (≥-2)**	0.61 (0.197-1.959)	0.4	0.916 (0.232-3.627)	0.9
delta basal T3-1 (>0.068**)	2.112 (0.565-7.901)	0.3	2.341 (0.577-9.494)	0.2

T1 = day 1-2 (24-48h), T2 = day 3-4 (72-96h) and T3 = day 5-6 (120-144h) after ICU admission. Delta was calculated as: (mitochondrial parameter at T3 minus T1); HR = hazard ratio; 95% CI = 95% confidence interval; BMI = body mass index; APACHE II = Acute Physiology And Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; basal = basal respiration (measured in nmol O2/min/10^7);
** p-value <0.05;*
*** including negative values (=a decrease in SOFA score or basal respiration, respectively, over time);*
Multivariable Cox regression analyses were performed using the Enter and Forward Stepwise Wald methods.

Discussion

In this prospective observational study, we found a significant increase in basal and ATP-linked respiration and coupling efficiency in sepsis patients compared to controls within the first week of ICU admission. This observation contrasted our hypothesis, as we did not demonstrate a decrease in PBMC mitochondrial respiration during sepsis. Moreover, a more significant increase in basal and ATP-linked respiration was observed during the first week of ICU stay in non-survivors compared to survivors ($p<0.05$), although these respiration parameters were not statistically different between the sepsis and control patients at baseline measurements. This progression of basal respiration was associated with the primary endpoint of 3-month mortality after correction for relevant covariates.

Therefore, the current results suggest that the upregulation of basal respiration may serve as a proxy marker for sepsis severity and outcomes.

Our findings are consistent with those of Sjövall *et al.* and Belikova *et al.*, who also found that basal mitochondrial respiration in PBMCs was significantly increased within the first 48 hours of ICU admission [6,19]. In addition, Sjövall *et al.* demonstrated a progressive increase in basal and maximal respiration during the first week of sepsis patients compared to healthy controls [19]. Strikingly, they observed no differences between surviving and non-surviving patients at any point in time. Both their inclusion and mortality rates were lower than in the present study, which may have led the study to be underpowered for differentiation between survivors and non-survivors. However, their article does neither report the original data nor p-values for the comparisons, so this claim cannot be substantiated.

In contrast with our findings, Jang *et al.* (studying mitochondrial respiration of PBMCs in 10 septic patients measured once shortly after presentation to an emergency department), Japiassú *et al.* (studying mitochondrial respiration of PBMCs in 20 patients during the first 48 hours of septic shock) and Garrabou *et al.* (studying mitochondrial respiration in 19 septic patients, time of measurement not mentioned) observed a significant reduction of ADP-linked respiration in permeabilized PBMCs of septic patients compared to controls [7,8,18]. In addition, in the study of Japiassú *et al.*, a significant reduction was observed in ADP-linked respiration in non-surviving sepsis patients compared with the postoperative controls without sepsis (5.60 versus 9.89 nmol O_2/min/10^7, respectively, $p < 0.01$). Survivors demonstrated a 2.9x increase in ATP-linked respiration after one week [7]. Contrastingly, we did not observe a significant change in respiratory function over time in survivors. Instead, we found a significant increase in basal and ATP-linked respiration in non-survivors during the first week of ICU stay.

These contradictory observations may be due to methodological variety. A clear difference between the abovementioned studies is the composition of the control group, which may influence the outcomes of comparisons between sepsis and control groups. In the current study, we chose to include sex- and age-matched controls since those are two factors known to influence mitochondrial respiratory function, which has not been done in other studies besides the study of Garrabou *et al.* [8]. Moreover, we selected metabolically healthy age- and sex-matched controls visiting the outpatient clinic. In contrast, Japiassú *et al.* included critically ill postoperative ICU patients, whereas Jang *et al.* chose to use three unmatched control groups of younger, older and infected (but not septic) patients [7,18]. It is intriguing that Sjövall *et al.* and our study still proved an increase in mitochondrial function parameters in PBMCs of septic patients, even though healthy controls were included [19].

Secondly, exclusion criteria differ between mentioned studies. We excluded many common comorbidities known to affect mitochondrial respiratory function (such as diabetes mellitus and COPD), which allowed us to exclude the potential confounding effect of these comorbidities. Such exclusion criteria were not reported in other studies.

Thirdly, the time at which the PBMCs were collected and measured respiration differed between studies. The timing of blood collection is not described by Garrabou *et al.* [8]. Jang *et al.* collected blood samples from patients with sepsis or septic shock upon presentation to the emergency department [18], whereas our measurements and those of Japiassú *et al.* commenced within 48 hours of ICU admission [7]. These may be very different (metabolic) time points in a patient's journey. Furthermore, our cohort was slightly older than those of Jang and Garrabou and their coworkers (68 vs 63, resp. 64 years of age), and although SOFA scores were similar in all studies, it is unknown whether all patients in the Garrabou and Jang cohorts required ICU admission.

Fourthly, the methods of respiration measurement vary in comparison with current literature. The current study resuspended PBMCs in a standardized medium, not plasma. This was similar to Japiassú *et al.* [7]. On the contrary, Sjövall and coworkers used the patient's plasma [19]. However, mitochondrial function in PBMCs is altered by plasma, as was demonstrated by Belikova co-workers [6]. Consequently, it is difficult to disentangle the effects of sepsis on plasma content from the effect of sepsis on mitochondria in PBMCs per se. Strikingly, in the current study, decreased mitochondrial respiration was, in fact, not visible. This approach revealed that the mitochondria of PBMCs are not dysfunctional and capable of improving respiratory function. In addition, this suggests that if a worsened respiratory function is observed in PBMCs of septic patients, this is perhaps more likely to originate from potential dysregulating components present in plasma. In addition, in some studies, PBMCs were permeabilized, while we used non-permeabilized PBMCs for respiratory measurements [7,8]. It could be hypothesized that this explains the differences with our results. However, since both Sjövall and Jang *et al.* have performed their measurements in both permeabilized and non-permeabilized PBMCs and found consistent results between those experiments, this is unlikely to explain the contrasting results with our studies.

Lastly, it can be hypothesized that the differences in respiratory function of PBMCs belonging to the different groups of our study are caused by a shift in PBMC composition rather than a shift in mitochondrial function per se. In humans, PBMC cell ratios vary across individuals, but typically, lymphocytes are in the range of 70–90 %, monocytes from 10 to 20 %, while dendritic cells are rare, accounting for only 1–2 % [17]. In our cohort, the PBMC lymphocyte-monocyte ratio (LMR) was lower in sepsis patients than in controls. This lower count is to be expected, as a lower LMR is associated with systemic

inflammation [25]. However, parameters of mitochondrial function did not correlate with the LMR, nor did the LMR change over time, and also not if more specific survivors versus non-survivors were compared (**Table 2**). We only found a significant correlation between proton leak and LMR on T3 (**Supplement 5)**. A similar correlation, or trend, was not found at any other time point or concerning another parameter. Therefore, we caution against interpretation at this time, as it goes beyond the scope and likely the power of the current study. However, it could still be of interest to measure mitochondrial function in distinct cell populations in future studies and should perhaps be considered when leukocytes are used as bioenergetic biomarkers [26].

Although we could not identify consistent methodological differences among all the studies mentioned, combining these methodological differences can contribute to the contrasting results.

Previous studies, although few, measuring mitochondrial function in muscle tissue of different origins have consistently reported a lower activity of mitochondrial complexes and a lower ATP content, concomitant with an altered expression of genes involved in regulating mitochondrial dynamics [15,22,23]. In the current study, mitochondrial function was measured in PBMCs. PBMCs are easily and non-invasively obtained. However, PBMCs are important cells during inflammation and systemic infection and may have a different metabolic response to sepsis compared to other tissues directly involved in multiorgan failure, such as the liver and muscles. Based on the results of the current study and in comparison to studies performed using skeletal muscle biopsies, PBMCs do not necessarily reflect the decrease in mitochondrial function, which is reported elsewhere in the body. Indeed, Jeger *et al.* reported that results from previous animal and clinical studies investigating mitochondrial function in several tissue types during sepsis are heterogeneous, reporting increased and decreased mitochondrial oxygen consumption [24]. Although speculative, these differences in mitochondrial functioning between tissues may reflect differences in their role during sepsis.

Thus, the increased basal and ATP-linked respiration as found in the current study may reflect an increased ATP demand of PBMCs during human sepsis, as a result of an activation of the immune system to combat the underlying infection. The clinical relevance of this increase is suggested by the higher increase in basal and ATP-linked respiration over time (i.e., between T1 and T3) in non-survivors, compared to survivors. Our findings may thus contrast speculation that mitochondrial dysfunction is the root cause of immunoparalysis and could be responsible for the onset of organ dysfunction[27]. Still, pathophysiological interpretation of this difference between survivors and non-survivors is precarious. The higher increase over time may, partially, be due to a lower basal and ATP-linked respiration in PBMC's at T1 of non-survivors

compared to survivors, although this was not statistically significant. Thus, a delayed up-regulation of PBMC activation in PBMCs of non-survivors compared to survivors, cannot fully be excluded but, in view of the lack of statistical significance, is highly speculative. Still, disregarding possible differences at T1, a higher increase in both respiration parameters over time could reflect differences in the development of the infection, or indicate immune dysfunctioning. This study does not provide clarity in this respect, especially since immune mechanisms during sepsis are complex, consisting of simultaneous hyperinflammation and immune suppression. Future studies, however, will take these hypotheses into account.

Progress and issues

We encountered several issues that delayed the study's progression beyond the expected inclusion period. In more sepsis patients than anticipated in advance, we could not perform all three measurements, primarily due to patients succumbing to their disease. Furthermore, not all measurements were successful. Inclusions were temporarily halted during the SARS-CoV-2 pandemic, as the university laboratory was closed during lockdowns. Inclusion of controls proved more difficult than anticipated due to the extensive list of exclusion criteria (mainly diabetes mellitus and COPD). Including older control patients was incredibly challenging, as they more often had comorbidities or refused the burden of participation.

Strengths

The consecutive measurements at three moments during the first week of ICU admission with fixed intervals are considered a strength of this study. This enabled us to better understand the progress of mitochondrial respiration during the first week of ICU admission in septic patients. In addition, the extensive list of exclusion criteria based on common comorbidities (e.g., diabetes mellitus and COPD) known to affect metabolism and mitochondrial function is a unique strength of this study, as this allowed us to exclude potential confounding effects of these comorbidities.

Limitations

The current study is limited by its single-centre design. However, as the samples needed to arrive at the laboratory in a fresh state, the hospital's proximity to a university laboratory equipped with an Oroboros was an essential condition for this study. Secondly, the possible effects of administered medication on mitochondrial function may represent an unaccounted confounder. Thirdly, multivariate Cox regression analyses found an association between the delta basal respiration and ICU and 3-month mortality, not the severity-of-disease score APACHE II. This may be due to additional confounding factors, which were not accounted for (residual confounding) or multicollinearity, although the VIF was low (<2).

Future directions

Further research is needed to elucidate the role of mitochondria in the sepsis pathophysiology. First, more extensive multicentre trials are needed to consolidate the current study's findings. It would be interesting to measure mitochondrial respiratory function in various other tissues in parallel to create more insight into the potential role of PBMCs as a proxy marker for mitochondrial respiratory function in other tissues. Furthermore, new studies investigating the progression of mitochondrial function over time in several tissues are warranted, including (progression of) gene expression involved in oxidative phosphorylation subunits and mitochondrial biogenesis.

Conclusion

This study demonstrated a higher basal and ATP-linked respiration in PBMCs within the first week of ICU admission in sepsis patients compared to their healthy matched controls. In addition, a progressive increase of basal and ATP-linked mitochondrial respiration in PBMCs during the first week of ICU stay was negatively associated with 3-month mortality.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10.
2. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis. Crit Care. 2020 May 19;24(1):239.
3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020 Jan 18;395(10219):200-211.
4. Yende S, Austin S, Rhodes A, Finfer S, Opal S, Thompson T, et al. Long-Term Quality of Life Among Survivors of Severe Sepsis: Analyses of Two International Trials. Crit Care Med. 2016 Aug;44(8):1461-7.
5. Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. Crit Care. 2015;19 Suppl 3(Suppl 3):S6.
6. Belikova I, Lukaszewicz AC, Faivre V, Damoisel C, Singer M, Payen D. Oxygen consumption of human peripheral blood mononuclear cells in severe human sepsis. Crit Care Med. 2007 Dec;35(12):2702-8.
7. Japiassú AM, Santiago AP, d'Avila JC, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, et al. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity. Crit Care Med. 2011 May;39(5):1056-63.
8. Garrabou G, Morén C, López S, Tobías E, Cardellach F, Miró O, et al. The effects of sepsis on mitochondria. J Infect Dis. 2012 Feb 1;205(3):392-400.
9. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence. 2014 Jan 1;5(1):66-72.
10. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. Biochim Biophys Acta Mol Basis Dis. 2017 Oct;1863(10 Pt B):2534-2545.
11. Brand MD, Nicholls DG. Assessing mitochondrial dysfunction in cells. Biochem J. 2011 Apr 15;435(2):297-312.
12. Supinski GS, Schroder EA, Callahan LA. Mitochondria and Critical Illness. Chest. 2020 Feb;157(2):310-322.
13. Singer M. Critical illness and flat batteries. Crit Care. 2017 Dec 28;21(Suppl 3):309.
14. Exline MC, Crouser ED. Mitochondrial mechanisms of sepsis-induced organ failure. Front Biosci. 2008 May 1;13:5030-41.
15. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002 Jul 20;360(9328):219-23.
16. Gründler K, Angstwurm M, Hilge R, Baumann P, Annecke T, Crispin A, et al. Platelet mitochondrial membrane depolarization reflects disease severity in patients with sepsis and correlates with clinical outcome. Crit Care. 2014 Feb 12;18(1):R31.
17. Kleiveland CR. Peripheral Blood Mononuclear Cells. In: Verhoeckx K, Cotter P, López-Expósito I, et al., editors. The Impact of Food Bioactives on Health: in vitro and ex vivo models [Internet]. Cham (CH): Springer; 2015. Chapter 15. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500157/ doi: 10.1007/978-3-319-16104-4_15.

18. Jang DH, Orloski CJ, Owiredu S, Shofer FS, Greenwood JC, Eckmann DM. Alterations in Mitochondrial Function in Blood Cells Obtained From Patients With Sepsis Presenting to an Emergency Department. Shock. 2019 May;51(5):580-584.
19. Sjövall F, Morota S, Persson J, Hansson MJ, Elmér E. Patients with sepsis exhibit increased mitochondrial respiratory capacity in peripheral blood immune cells. Crit Care. 2013 Jul 24;17(4):R152.
20. Clere-Jehl R, Helms J, Kassem M, Le Borgne P, Delabranche X, Charles AL, Geny B, Meziani F, Bilbault P. Septic Shock Alters Mitochondrial Respiration of Lymphoid Cell-Lines and Human Peripheral Blood Mononuclear Cells: The Role of Plasma. Shock. 2019 Jan;51(1):97-104.
21. Silaidos C, Pilatus U, Grewal R, Matura S, Lienerth B, Pantel J, et al. Sex-associated differences in mitochondrial function in human peripheral blood mononuclear cells (PBMCs) and brain. Biol Sex Differ. 2018 Jul 25;9(1):34.
22. Fredriksson K, Tjäder I, Keller P, Petrovic N, Ahlman B, Schéele C, et al. Dysregulation of mitochondrial dynamics and the muscle transcriptome in ICU patients suffering from sepsis induced multiple organ failure. PloS one. 2008;3(11):e3686.
23. Fredriksson K, Hammarqvist F, Strigård K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. Am J Physiol Endocrinol Metab. 2006 Nov;291(5):E1044-50.
24. Jeger V, Djafarzadeh S, Jakob SM, Takala J. Mitochondrial function in sepsis. Eur J Clin Invest. 2013 May;43(5):532-42.
25. Gerratana L, Basile D, Toffoletto B, Bulfoni M, Zago S, Magini A, et al. Biologically driven cut-off definition of lymphocyte ratios in metastatic breast cancer and association with exosomal subpopulations and prognosis. Sci Rep. 2020 Apr 24;10(1):7010.
26. Kramer PA, Ravi S, Chacko B, Johnson MS, Darley-Usmar VM. A review of the mitochondrial and glycolytic metabolism in human platelets and leukocytes: implications for their use as bioenergetic biomarkers. Redox Biol. 2014 Jan 10;2:206-10.
27. Nedel W, Deutschendorf C, Portela LVC. Sepsis-induced mitochondrial dysfunction: A narrative review. World J Crit Care Med. 2023 Jun 9;12(3):139-152.

Supplemental material

Supplement 1. Progression of mitochondrial function in early sepsis (n=40) and controls (n=26)

	Controls (n=26)	Sepsis patients (n=40[a])						
		T1 (n=38)		p-value[b]	T2 (n=35)	p-value[c]	T3 (n=28)	p-value[d]
basal respiration, nmol O_2/min/10^7	2.24 [1.67-3.58]	4.27 [2.70-6.07]		0.014*	4.83 [3.09-8.06]	0.9	4.73 [2.23-6.89]	0.5
proton leak, nmol O_2/min/10^7	0.84 [0.67-1.74]	1.79 [1.07-2.56]		0.2	1.54 [1.12-2.39]	0.6	1.51 [0.74-2.12]	0.9
maximal respiration, nmol O_2/min/10^7	5.05 [3.73-7.79]	8.32 [6.19-13.95]	n=37	0.053	9.90 [7.13-17.52]	0.9	10.03 [3.90-15.85]	0.6
ATP-linked respiration, nmol O_2/min/10^7	1.37 [0.75-2.02]	2.84 [1.32-4.04]	n=37	0.006*	3.01 [1.90-5.08]	0.7	3.11 [1.55-5.03]	0.1
SRC, nmol O_2/min/10^7	2.77 [2.04-4.41]	4.47 [2.74-7.13]	n=37	0.1	4.34 [3.49-8.44]	1.0	4.86 [1.96-8.89]	0.8
coupling efficiency (%)	59.9 [46.8-67.4]	63.5 [50.5-72.4]	n=37	0.048*	66.6 [58.4-72.7]	0.5	69.9 [63.0-74.8]	0.051

[a] Unless stated otherwise due to missing variables;
[b] T1 compared to the control group; p-values were calculated using the Wilcoxon signed rank test;
[c] T1 compared to T2, p-values were calculated using the Wilcoxon signed rank test;
[d] T1 compared to T3, p-values were calculated using the Wilcoxon signed rank test;
** p-value <0.05.*
T1 = day 1-2 (24-48h); T2 = day 3-4 (72-96h); T3 = day 5-6 (120-144h) after ICU admission; ATP-linked respiration = basal respiration minus proton leak; SRC = spare respiratory capacity = maximal respiration minus basal respiratory capacity; coupling efficiency = ATP-linked respiration divided by basal respiration. All values are reported as medians with interquartile ranges.

Supplement 2. Mitochondrial function over time in survivors (A; n=26) and non-survivors (B; n=14) at different time points

	T1				T2				T3			
	survivors (n=26)		non-survivors (n=12)	p	survivors (n=22)		non-survivors (n=13)	p	survivors (n=15)	non-survivors (n=13)		p
basal respiration	4.52 [3.43-8.63]		3.16 [2.37-5.58]	0.2	4.40 [3.01-8.38]		4.99 [3.15-7.89]	0.8	3.76 [2.13-6.95]	4.80 [2.48-6.94]		0.9
proton leak	2.04 [1.28-2.90]		1.14 [0.86-1.97]	0.048*	1.54 [1.01-2.09]		1.54 [1.33-2.88]	0.4	1.42 [0.79-2.14]	1.74 [0.64-2.27]		0.6
maximal respiration	8.49 [6.81-15.35]	n=25	6.93 [4.68-12.75]	0.2	8.28 [7.08-17.90]		10.69 [5.05-17.64]	0.6	9.20 [3.89-15.13]	10.86 [2.87-16.86]		0.9
ATP-linked respiration	2.89 [1.58-5.33]	n=25	2.16 [1.27-3.59]	0.3	2.89 [1.83-5.61]		3.01 [1.82-5.32]	0.9	3.11 [1.53-5.57]	3.11 [1.87-4.95]		0.9
SRC	4.56 [2.92-7.13]	n=25	4.00 [2.20-7.17]	0.5	4.03 [3.39-8.61]		6.14 [2.18-9.85]	0.6	4.64 [1.89-8.25]	6.06 [1.24-9.92]		0.7
coupling efficiency (%)	64.0 [50.5-72.3]	n=24	62.7 [50.4-73.1]	1.0	67.2 [60.5-72.7]	n=21	62.9 [53.5-71.1]	0.2	68.7 [61.7-74.6]	71.3 [67.0-75.4]	n=12	0.4

*T1 = day 1-2 (24-48h); T2 = day 3-4 (72-96h); T3 = day 5-6 (120-144h) after ICU admission; ATP-linked respiration = basal respiration minus proton leak; SRC = spare respiratory capacity = maximal respiration minus basal respiratory capacity; coupling efficiency = ATP-linked respiration divided by basal respiration. All values are reported as medians with interquartile ranges. * p-value <0.05.*

Supplement 3. Comparison of mitochondrial function comparing time points during early sepsis among survivors (A) and non-survivors (B) (mortality at 3-months)

A.

Survivors	T1 versus T2 p-value	T1 versus T3 p-value
basal respiration	0.2	0.3
proton leak	0.073	0.3
maximal respiration	0.4	0.3
ATP-linked respiration	0.6	0.7
SRC	0.6	0.3
coupling efficiency (%)	0.2	0.4

B.

Non-survivors	T1 versus T2 p-value	T1 versus T3 p-value
basal respiration	0.2	0.033*
proton leak	0.2	0.1
maximal respiration	0.4	0.075
ATP-linked respiration	0.2	0.004*
SRC	0.4	0.1
coupling efficiency (%)	0.6	0.008*

*T1 = day 1-2 (24-48h); T2 = day 3-4 (72-96h); T3 = day 5-6 (120-144h) after ICU admission; ATP-linked respiration = basal respiration minus proton leak; SRC = spare respiratory capacity = maximal respiration minus basal respiratory capacity; coupling efficiency = ATP-linked respiration divided by basal respiration. P-values were calculated using the Wilcoxon signed rank test; * p-value <0.05.*

Supplement 4. Patient outcomes compared between survivors (n=26) and non-survivors (n=14)

	Survivors	Non-survivors	p-value
ICULOS, days	8 [6-25]	9 [7-16]	0.6
HLOS, days	20 [11-30]	15 [10-24]	0.3
Duration of ventilation, days	4 [1-15]	5 [2-9]	1.0

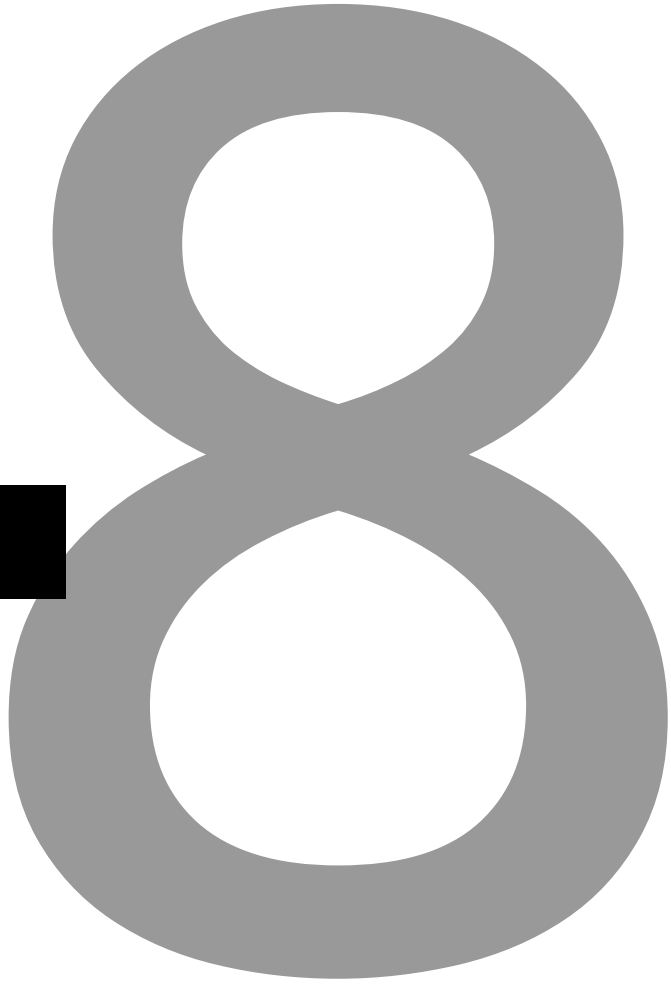
ICULOS = intensive care unit length of stay; HLOS = hospital length of stay;
All values are reported as medians with interquartile ranges. P-values were calculated using the Mann-Whitney U test.

Supplement 5. ANOVA analysis for the association of secondary endpoints duration of mechanical ventilation (A), ICU lengths of stay (B), and hospital length of stay (C), baseline and clinical characteristics and mitochondrial respiratory function (n=40)

	beta	SE	p-value
A. Duration of mechanical ventilation			
Sex (female)	0.923	4.825	0.9
BMI (>25.7)	-5.209	3.846	0.19
APACHE II on admission (>18)	6.702	3.995	0.109
delta SOFA T3-1 (≥-2)	3.198	4.369	0.5
delta basal T3-1 (>0.068**)	-4.417	4.065	0.3
B. ICU length of stay			
Sex (female)	-0.677	5.059	0.9
BMI (>25.7)	-2.357	4.033	0.6
APACHE II on admission (>18)	6.039	4.189	0.16
delta SOFA T3-1 (≥-2)	5.118	4.581	0.3
delta basal T3-1 (>0.068**)	-4.402	4.262	0.3
C. HOS length of stay			
Sex (female)	1.851	6.736	0.8
BMI (>25.7)	-9.363	5.369	0.097
APACHE II on admission (>18)	7.342	5.577	0.2
delta SOFA T3-1 (≥-2)	1.331	6.099	0.8
delta basal T3-1 (>0.068**)	-6.356	5.675	0.3

T1 = day 1-2 (24-48h), T2 = day 3-4 (72-96h) and T3 = day 5-6 (120-144h) after ICU admission. Delta was calculated as: (mitochondrial parameter at T1 minus T3);
SE = standard error; BMI = body mass index, APACHE II = Acute Physiology And Chronic Health Evaluation; SOFA = sequential organ failure assessment, basal = basal respiration (measured in nmol O2/min/10^7);
** p-value <0.05;*
*** including negative values (=a decrease in SOFA score or basal respiration, respectively, over time).*

CHAPTER 8



Association between first-week propofol administration and long-term outcomes of critically ill mechanically ventilated patients: a retrospective cohort study

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Abstract

Background & Aim

Propofol is commonly used in ICUs, but its long-term effects have not been thoroughly studied. In vitro studies suggest it may harm mitochondrial function, potentially affecting clinical outcomes. This study aimed to investigate the association between substantial propofol sedation and clinical outcomes in critically ill patients.

Methods

We conducted a single-centre cohort study of critically ill, mechanically ventilated (≥7 days) adults to compare patients who received a substantial dose of propofol (cumulative >500mg) during the first week of ICU admission with those who did not. The primary outcome was the association between substantial propofol administration and 6-month mortality, adjusted for relevant covariates. Subanalyses were performed for administration in the early (day 1-3) and late (day 4-7) acute phases of critical illness due to the metabolic changes in this period. Secondary outcomes included tracheostomy need and duration, length of ICU and hospital stay (LOS), discharge destinations, ICU, hospital, and 3-month mortality.

Results

A total of 839 patients were enrolled, with 73.7% receiving substantial propofol administration (substantial propofol dose group). Six-month all-cause mortality was 32.4%. After adjusting for relevant variables, we found no statistically significant difference in 6-month mortality between both groups. There were also no significant differences in secondary outcomes.

Conclusion

Our study suggests that substantial propofol administration during the first week of ICU stay in the least sick critically ill, mechanically ventilated adult patients is safe, with no significant associations found with 6-month mortality, ICU- or hospital LOS, differences in discharge destinations or need for tracheostomy.

Introduction

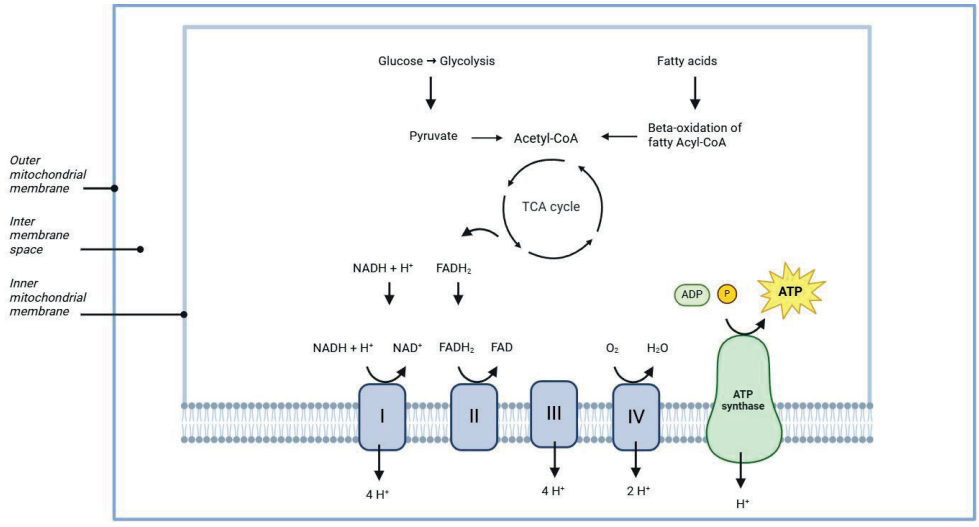
Propofol (2,6-diisopropyl phenol) is an intravenously administered sedative-hypnotic agent, that also can be considered as parenteral nutrition as it is dissolved in a high-caloric lipid emulsion. Due to its favourable pharmacological properties, including a fast onset and offset of action, it is frequently used in critically ill patients admitted to the Intensive care unit (ICU) to reduce anxiety and agitation, promote tolerance of mechanical ventilation, and prevent auto-extubation [1-5].

However, propofol also has the potential for severe side effects [6]. As such, prolonged or high-dose use of propofol (>4-5mg/kg*h or >48 hours) may lead to a life-threatening condition known as propofol infusion syndrome (PRIS) [7-10]. PRIS can manifest in various ways among patients and ultimately result in multiple organ failure [4,7,8,10-13]. While its exact pathophysiology is not yet understood, several studies suggest that propofol-induced suppression of mitochondrial function plays a pivotal role. This makes patients with pre-existing mitochondrial diseases particularly vulnerable to this syndrome [12-15].

Mitochondrial (dys)function in health and sepsis

Mitochondria, known as the cell powerhouses, primarily produce energy through the oxidative phosphorylation process (see **Figure 1**) . In health, acetyl coenzyme A (Acetyl-CoA), derived from glycolysis as pyruvate and the beta-oxidation of fatty acids, is oxidised in the citric acid cycle to carbon dioxide and water. This process generates an electrochemical gradient that is used to phosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) by moving electrons across the mitochondrial electron transport chain (ETC) at the inner mitochondrial membrane [13,16-19].

Figure 1. Simplified schematic overview of ATP production in a mitochondrion via the process of oxidative phosphorylation



Acetyl-CoA = acetyl coenzyme A; ADP = adenosine diphosphate; ATP = adenosine triphosphate; FADH = flavin adenine dinucleotide (FAD) + hydrogen (H); NADH = nicotinamide-adenine dinucleotide (NAD) + hydrogen (H); TCA = tricarboxylic acid cycle.
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During the early stages of sepsis, a general dysfunction of mitochondria has been observed [18-23]. Persistent mitochondrial dysfunction during critical illness has been associated with ICU-acquired weakness (ICU-AW) and prolonged muscle weakness after ICU discharge [24,25].

Propofol-induced mitochondrial dysfunction

Propofol may adversely affect mitochondrial functioning. Studies in animal models and human skeletal muscle cells suggest a disruptive effect on the oxidative phosphorylation process described above [10,12,15,26-30]. Furthermore, propofol-induced apoptosis has been demonstrated in patients with pre-existing mitochondrial dysfunction or using biguanide drugs such as metformin [9]. Altogether this may worsen sepsis-induced bioenergetic downregulation, aggravating multiple organ failure and thus influencing clinical outcomes [16-18,31-34].

Additional effects of propofol influencing outcomes

In addition, an increased risk of healthcare-related infections due to the lipophilic nature of propofol formulations has been reported, favouring bacterial growth at room temperature [35]. However, propofol's beneficial immunomodulating effects have also been observed, such as anti-inflammatory and antioxidant properties [36-38].

Long-term effects of propofol

Despite its routine use in the ICU, the long-term effects of propofol used for sedation in critically ill patients have not been studied well. Very recently, Kotani and coworkers conducted a meta-analysis of randomised controlled trials (RCTs) studying all-cause mortality in postoperative and critically ill patients receiving propofol versus any other sedative agent [5]. No significant difference in mortality was observed in the ICU patient group (52/252 of studies, 21%).

To address the lack of knowledge regarding the long-term effects of substantial propofol use, this study aimed to investigate its potential negative impact on clinical outcomes. Although mitochondrial function could not be measured in this retrospective study, the hypothesis was that propofol's adverse effects on mitochondria could worsen clinical outcomes, such as mortality and ICU-AW, as well as discharge destination. The study analyzed the association between 6-month mortality and patients who received a substantial dose of propofol for an extended period (>500mg cumulative dose) during the first week of ICU admission and those who did not. The cut-off value of 500mg was intentionally chosen to distinguish patients who received a substantial dose of propofol from patients who received no propofol or only a small dose periprocedural considering that such a small dose would likely not affect clinical endpoints. The no substantial propofol dose group included patients who received a small dose of propofol for intubation or other short procedures only. In the group who received a substantial dose of propofol, subanalyses were performed for administration in the early (day 1-3) and late (day 4-7) acute phases of critical illness due to the metabolic changes in this period (endogenous energy production, bio-energetic downregulation) The study's secondary outcomes were ICU and hospital LOS, duration of mechanical ventilation, the need for a tracheostomy to wean from mechanical ventilation, discharge destinations, and ICU, hospital, and 3-month mortality.

Materials and methods

Study design & participants

We conducted a retrospective observational single-centre cohort study on adult patients (aged ≥18 years) who were mechanically ventilated for ≥7 days and admitted between January 1st 2011, and May 31st 2021, to the mixed medical-surgical ICU of Gelderse Vallei hospital (ZGV, Ede, The Netherlands).

Patients with neuromuscular or mitochondrial diseases or a pre-existent need for dialysis were excluded, as were patients with incomplete sedative or nutritional provision data, contraindications to full nutrition, or who started mechanical ventilation more than 48

hours after ICU admission. Patients who were transferred from another hospital were also excluded. Only the first admission was evaluated for patients with ICU readmission within six months after discharge.

Sedation protocol

All patients were sedated using either propofol and/or midazolam and received concomitant analgesia (remifentanil or fentanyl) as per our local ICU protocol. The sedative medication was titrated using the Richmond Agitation Sedation Scale (RASS; target -2 to 0) and interrupted daily whenever possible through a wake-up call.

Substantial propofol doses versus no substantial propofol doses study groups

To assess the long-term effects of substantial propofol use, all eligible patients were divided into two groups: patients who received a substantial dose of propofol (hereafter: 'substantial propofol dose group') were compared to patients who did not. Substantial propofol administration was defined as a cumulative propofol dose of >500 milligrams during the first week of ICU stay. This cut-off value was chosen intentionally (being about 2.5 vials of 200mg propofol) to distinguish patients who received a substantial dose of propofol from patients who received no propofol or only small doses periprocedural; these latter patients were analyzed in the no substantial propofol dose group.

Study endpoints

The primary outcome was 6-month mortality. In the substantial propofol group, we also examined the association between the primary outcome and propofol administration given during the early and late acute phases, respectively, due to the metabolic changes expected in these periods. In the acute phase of critical illness there is an enormous endogenous energy production, and, at the same time, demands are lower as the body's metabolism is downregulated. It is thought that mitochondria are more vulnerable and cannot utilise substrates in this phase [22]. Secondary study parameters included duration of mechanical ventilation, need for a tracheostomy to wean from mechanical ventilation, ICU and hospital LOS, discharge destinations, and ICU, in-hospital, and 3-month mortality.

Data collection

Data collection from the electronic Patient Data Management System (PDMS) included patient characteristics (gender, age, anthropometry, comorbidities), admission type, several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), modified Nutrition Risk In Critically ill (mNUTRIC), Charlson Comorbidity Index (CCI)), laboratory values, (non-)nutritional intake (including enteral/parenteral nutrition (EN/PN)), outcome parameters such

as duration of mechanical ventilation, length of ICU and hospital stay, discharge destination, and readmission rates. Data regarding propofol use was collected from the precise and automated recording of all individual non-nutritional calorie infusions from glucose, citrate and propofol for the first seven days after ICU admission. The amount of non-nutritional calories from propofol was used to calculate the exact daily and cumulative dosages of propofol (one millilitre (10mg/mL) propofol contains 1.1 kilocalories). Moreover, the use of sedative and neuromuscular blocking agents was recorded. Finally, data collection included nutritional intake and achievement of energy and protein targets, as it has been demonstrated that macronutrient intake impacts clinical outcomes, particularly protein intake [39-45].

Data extraction was performed using queries searching the ICU PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (NeoZis; MI Consultancy, Katwijk, The Netherlands). The National Population Register was consulted for death records. Data verification was conducted manually. All parameters of interest had been routinely collected during standard clinical care and therefore imposed no burden or risk to patients.

Nutritional support

All patients in our ICU received nutritional support according to our local ICU protocol (as proposed by Van Zanten *et al.* [46]). Energy and protein targets were calculated by the dieticians using the Food and Agricultural Organization and World Health Organization (FAO/WHO/UNU) formulas, adapted for specific patient groups according to the local hospital protocol (see **Supplement 1**)[47]. The amount of intake (energy and proteins) was used to calculate the percentage of reached energy and protein targets (hereafter indicated with "adequacy").

Bodyweight was adjusted to ideal body weight (IBW) at a Body mass index (BMI) of 18.5 or 27 kg/m^2 in case of BMI <18.5 or > 27 kg/m^2.

Intake targets on the day of ICU discharge were adjusted for the actual time spent in the ICU that day. Days were defined as calendar days.

Statistical analysis

To analyse the data, continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on whether the data were parametric or non-parametric, respectively. Normality was examined both numerically and graphically. Discrete variables were reported as proportions.

To compare the baseline characteristics and outcomes between the substantial propofol and no substantial propofol dose groups, the chi-square test, independent samples t-test, and Wilcoxon rank sum test were used where appropriate.

After adjusting for relevant parameters, the primary outcome parameter was evaluated using Kaplan-Meier curves and uni- and multivariable Cox proportional hazards regression models.

As appropriate, Cox, linear, or logistic regression models were used for secondary outcome parameters. Multivariable Cox regression analyses were conducted using the Enter and Forward (Stepwise Wald) methods. Variables were dichotomised based on median values in case of non-linearity (by visual assessment of boxplots).

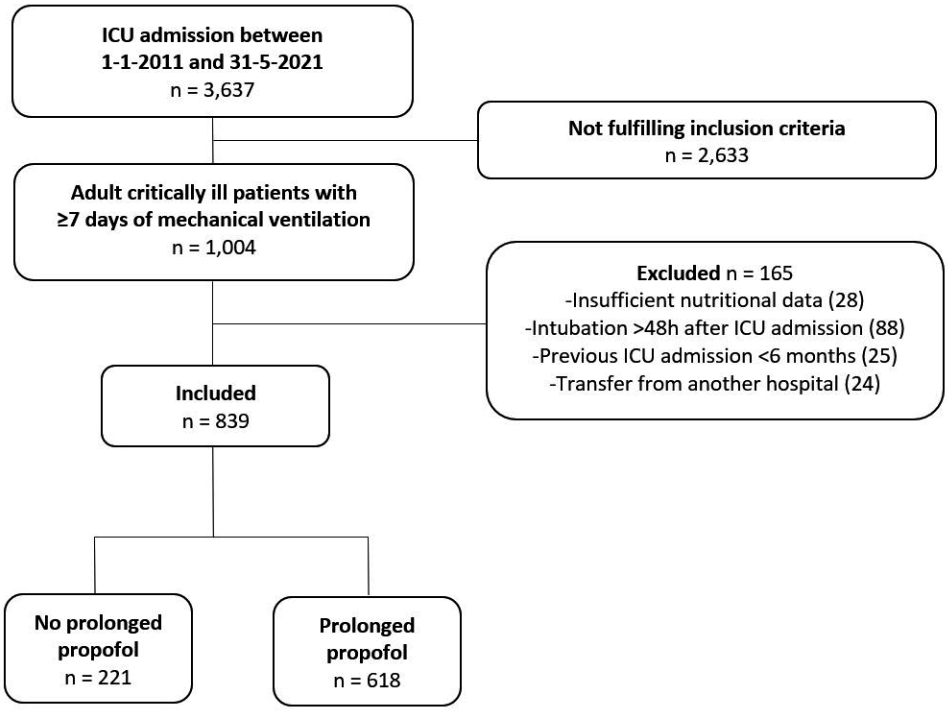
The variables age, gender, BMI, APACHE II and mNUTRIC scores, CCI, sepsis on admission, administration of parenteral nutrition, and energy and protein adequacies were analyzed in regression analyses based on literature and clinical relevance. However, energy and protein adequacies were excluded from the analysis due to their strong correlation with the administration of PN during days 1-7. The variables age, APACHE II, and CCI were also omitted in the final regression models due to their overlap with the mNUTRIC score. BMI and protein adequacy were dichotomised due to their non-linear relationship with the outcome parameters.

The variance inflation factor (VIF) was used to check for multicollinearity. A VIF value less than 2 was considered acceptable. All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, New York, United States of America, 2016). P-values less than 0.05 were considered statistically significant, while p-values less than 0.10 were considered trends.

Results

The study included 839 patients who met the eligibility criteria out of 3,637 patients admitted to the ICU between January 1st 2011, and May 31st 2021. These eligible patients were mechanically ventilated for seven days or more. Of the initial 1,004 patients who met the mechanical ventilation criteria, 165 were excluded based on predefined exclusion criteria.

Figure 2. Study flowchart



ICU = Intensive care unit; n = number of patients.

Table 1 presents the baseline characteristics of the study population. The median duration of mechanical ventilation was 11 days (IQR 8-17). About 16.9% of the patients received PN during their ICU stay. The mean daily energy and protein intake were 17.8 (SD 5.3) kcal/kg and 0.92 (SD 0.3) g/kg, respectively.

Table 1. Baseline characteristics

			Cumulative propofol dose day 1-7		
		All patients	**≤500mg**	**>500mg**	**p-value[a)]**
		(n=839)	***(n=221)***	***(n=618)***	
Gender (male)	*n (%)*	525 (62.6)	129 (58.4)	396 (64.1)	0.132
Age (years)	*mean (SD)*	66.4 (13.9)	70.1 (11.7)	65.2 (14.4)	<0.001*
BMI (kg/m^2)	*mean (SD)*	27.8 (5.8)	27.4 (5.8)	27.9 (5.8)	0.279
APACHE II score	*mean (SD)*	23.0 (7.0)	23.9 (7.2)	22.7 (6.9)	0.022*
SOFA score	*mean (SD)*	8.1 (3.1)	8.0 (3.5)	8.2 (2.9)	0.411
mNUTRIC score	*mean (SD)*	5.0 (1.8)	5.3 (2.0)	4.9 (1.8)	0.016*
Charlson Comorbidity Index	*mean (SD)*	3.8 (2.4)	4.5 (2.3)	3.6 (2.3)	<0.001*
Admission type (surgical)	*n (%)*	249 (29.7)	56 (25.3)	193 (31.2)	0.100
Sepsis on admission (yes) [n=838]	*n (%)*	348 (41.5)	126 (57.0)	222 (35.9)	<0.001*
Propofol administered (yes)	*n (%)*	712 (84.9)	68 (30.8)	618 (100)	<0.001*
Cumulative dose day 1-7 (mg)	*median [IQR]*	3005 [418-9909]	0 [0-145]	5855 [2452-13364]	<0.001*
>200mg	*n (%)*	657 (78.3)	64 (29)	618 (100)	
>500mg	*n (%)*	618 (73.7)	0 (0)	618 (100)	
>1000mg	*n (%)*	566 (67.5)	0 (0)	577 (93.4)	
Cumulative dose day 1-7 (mg/kg IBW)	*median [IQR]*	4.1 [0.5-13.4]	0 [0-0.2]	7.8 [3.3-17.1]	<0.001*
Muscle relaxants administered (yes)	*n (%)*	355 (42.3)	87 (39.4)	268 (43.4)	0.302
Number of days	*median [IQR]*	2 [1-4]	2 [1-4]	2 [1-4]	0.779

[a)] p-values were calculated using the chi-square test, independent samples t-test or Wilcoxon rank sum test where appropriate;

N = number of patients; SD = standard deviation; IQR = interquartile range; BMI = body mass index (on ICU admission); APACHE II = Acute Physiology and Chronic Health Evaluation II (on ICU admission); SOFA = Sequential Organ Failure Assessment (on ICU admission); mNUTRIC = modified Nutrition Risk in Critically Ill (on ICU admission); IBW = ideal body weight; ICU = intensive care unit;

** p-value < 0.05.*

Substantial versus no substantial dose of propofol

During the first seven days of ICU admission, 73.7% of the patients (n=618) received more than 500mg of propofol, categorising them as the 'substantial propofol dose group'. Compared to the 'no substantial propofol dose group', which received no or ≤500mg of propofol, the substantial dose group was younger (65.2 (SD 14.4) vs. 70.1 (SD 11.7) years, p<0.001), had fewer comorbidities (CCI 3.6 (SD 2.3) vs. 4.5 (SD 2.3), p<0.001), and were diagnosed with sepsis on admission less frequently (35.9 vs. 57.0% of cases, p<0.001). Additionally, the substantial propofol dose group had lower APACHE II (22.7 (SD 6.9) vs. 23.9 (SD 7.2), p=0.022) and mNUTRIC scores (4.9 (SD 1.8) vs. 5.3 (SD 2.0), p=0.016) on ICU admission. However, no significant differences in muscle relaxants or chronic steroid use were observed (p>0.05).

Sedative administration and nutritional assessment

The substantial propofol dose group received a median dose of 5,855 [IQR 2,452-13,364] mg of propofol during the first seven days of ICU admission, equivalent to 7.8 [3.3-17.1] mg/kg IBW (**Table 1**). Energy targets and intake were comparable between groups, but the substantial propofol dose group had a significantly higher load of non-nutritional kilocalories (median 2.6 [IQR 1.5-4.4] kcal/kg IBW*day versus median 1.1 [0.6-2.2] kcal/kg IBW*day in the no substantial propofol dose group, p<0.001) (**Supplement 2**). Although both groups had similar energy adequacies, there was a significant difference in protein intake (mean 0.90 (SD 0.3) versus 0.97 (SD 0.3) g/kg IBW*day, p=0.007) and day 1-7 protein adequacy (mean 72.0 (SD 23.4) versus 78.3% (SD 24.0), p=0.004) between the substantial propofol dose and no substantial propofol dose group, respectively.

Primary outcome: 6-month mortality

Six-month mortality was observed in 272 patients (32.4%). Univariable analysis revealed a statistically significant difference in mortality between the substantial propofol dose group and the no substantial propofol dose group (30.3% versus 38.5%, respectively; p=0.025; univariable Cox regression >500mg propofol: HR 0.753 (95% CI 0.582-0.973), p=0.030) (**Tables 2-3**).

Table 2. Clinical outcomes

			Cumulative propofol dose day 1-7		
		All patients	**≤500mg**	**>500mg**	**p-value[a)]**
		(n=839)	***(n=221)***	***(n=618)***	
Discharge destination	*n (%)*				0.026*
Transfer to another hospital		75 (8.9)	22 (10.0)	53 (8.6)	
Home		251 (29.9)	49 (22.2)	202 (32.7)	
Nursing home		150 (17.9)	41 (18.6)	109 (17.6)	
Rehabilitation centre		139 (16.6)	42 (19.0)	97 (15.7)	
Hospice		2 (0.2)	2 (0.9)	0 (0)	
Mortuary (in-hospital death)		213 (25.4)	63 (28.5)	150 (24.3)	
Else		9 (1.1)	2 (0.9)	7 (1.1)	
Mortality	*n (%)*				
ICU		145 (17.3)	47 (21.3)	98 (15.6)	0.068
In-hospital		213 (25.4)	63 (28.5)	150 (24.3)	0.214
3-month		258 (30.8)	83 (37.6)	175 (28.3)	0.011*
6-month		272 (32.4)	85 (38.5)	187 (30.3)	0.025*
Duration of MV (days)	*median [IQR]*	11 [8-17]	11 [8-17]	11 [8-17]	0.251
Need for a tracheostomy to wean (yes)	*n (%)*	200 (23.8)	56 (25.3)	144 (23.3)	0.542
Need for CRRT (yes)	*n (%)*	144 (17.2)	56 (25.3)	88 (14.2)	<0.001*
ICU LOS (TDA, days) [n=694]	*median [IQR]*	16 [11-27]	18 [13-29]	15 [11-27]	0.292

Table 2. Continued

			Cumulative propofol dose day 1-7		
		All patients	**≤500mg**	**>500mg**	**p-value[a)]**
Hospital LOS (TDA, days) [n=626]	*median [IQR]*	30 [21-46]	32 [23-45]	29 [21-47]	0.409
All-cause readmission <6 months [n=626]	*n (%)*				
To hospital		260 (41.5)	74 (33.5)	186 (30.1)	0.350
To ICU		38 (6.1)	15 (6.8)	33 (5.3)	0.426

a) p-values were calculated using the chi-square test or Wilcoxon rank sum test where appropriate;
n = number of patients; IQR = interquartile range; MV = mechanical ventilation; CRRT = continuous renal replacement therapy; ICU = intensive care unit; LOS = length of stay; TDA = time to alive discharge;
** p-value <0.05.*

Table 3. Univariable and multivariable COX regressions for the association of substantial propofol administration** and 6-month mortality

Day 1-7	**Univariable**		**Multivariable**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Propofol dose day 1-7 (>500mg)	0.753 (0.582-0.973)	0.030*	0.899 (0.689-1.175)	0.436
Gender (female)	0.905 (0.705-1.161)	0.431	0.891 (0.693-1.146)	0.369
BMI (>27 kg/m^2)	0.733 (0.577-0.930)	0.011*	0.710 (0.559-0.903)	0.005*
mNUTRIC score	1.386 (1.291-1.487)	<0.001*	1.379 (1.284-1.481)	<0.001*
Sepsis on admission (yes)	1.142 (0.899-1.451)	0.276	1.124 (0.8880-1.437)	0.348
Admission type (surgical)	0.996 (0.769-1.291)	0.976	0.909 (0.682-1.211)	0.514
PN administered days 1-7 (yes)	1.355 (1.012-1.815)	0.041*	1.167 (0.844-1.614)	0.350

HR = hazard ratio; 95% CI = 95% confidence interval; BMI = body mass index; mNUTRIC = modified Nutrition Risk in Critically Ill; PN = parenteral nutrition;
** p-value < 0.05;*
*** substantial propofol administration: >500mg during the first seven days of ICU admission;*
Multivariable Cox regression analyses were conducted using the Enter and Forward (Stepwise Wald) methods.

Cox regression

However, in the multivariable Cox regression model, no association between substantial propofol use and 6-month mortality was found. Only BMI (≤27 kg/m2) (HR 1.408, 95% CI 1.107-1.790, p=0.005) and mNUTRIC score (HR 1.379, 95% CI 1.284-1.481, p<0.001) remained significantly associated with 6-month mortality (**Table 3** and **Supplement 4**). The variables in this final model had a VIF of <2.

Substantial propofol dose group: propofol administered during the early (days 1-3) versus late (days 4-7) acute phases of critical illness

The association between the primary outcome of 6-month mortality and substantial propofol administration during the early (days 1-3) and late (days 4-7) acute phases was analyzed. In the early acute phase, no significant differences were observed between the substantial dose and no substantial propofol dose groups in uni- and multivariable

analyses. In the late acute phase, a survival benefit was observed for the group receiving >500mg propofol (HR 0.750, 95% CI 0.591-0.952, p=0.018), but this effect disappeared when corrected for other factors in the multivariable analysis (**Supplement 3**).

Secondary outcomes

An overview of the duration of mechanical ventilation and need for a tracheostomy to wean from mechanical ventilation, ICU and hospital LOS, discharge destinations, ICU readmission within six months, and ICU, in-hospital, and 3-month mortality for both substantial and no substantial propofol dose groups are shown in **Tables 2** and **4**.

Table 4. Univariable and multivariable regressions for the association of substantial propofol administration and secondary outcomes

A. ICU mortality

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Propofol dose day 1-7 (>500mg)	0.726 (0.513-1.028)	0.071	0.932 (0.648-1.340)	0.704
Gender (female)	0.865 (0.613-1.220)	0.407	0.844 (0.596-1.194)	0.338
BMI (>27 kg/m^2)	0.618 (0.443-0.862)	0.005*	0.603 (0.432-0.841)	0.003*
mNUTRIC score	1.389 (1.261-1.530)	<0.001*	1.376 (1.247-1.517)	<0.001*
Sepsis on admission (yes)	1.343 (0.969-1.860)	0.076	1.303 (0.933-1.820)	0.120
Admission type (surgical)	0.914 (0.637-1.312)	0.626	0.724 (0.482-1.087)	0.120
PN administered days 1-7 (yes)	1.726 (1.188-2.508)	0.004*	1.620 (1.063-2.467)	0.025*

B. In-hospital mortality

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Propofol dose day 1-7 (>500mg)	0.824 (0.614-1.106)	0.197	1.021 (0.751-1.387)	0.896
Gender (female)	0.937 (0.708-1.241)	0.651	0.931 (0.702-1.235)	0.62
BMI (>27 kg/m^2)	0.726 (0.554-0.951)	0.020*	0.699 (0.533-0.918)	0.010*
mNUTRIC score	1.444 (1.332-1.566)	<0.001*	1.446 (1.332-1.571)	<0.001*
Sepsis on admission (yes)	1.139 (0.869-1.493)	0.346	1.145 (0.868-1.510)	0.337
Admission type (surgical)	0.969 (0.722-1.300)	0.833	0.891 (0.643-1.235)	0.488
PN administered days 1-7 (yes)	1.316 (0.944-1.833)	0.105	1.130 (0.782-1.633)	0.515

C. Three-month mortality

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Propofol dose day 1-7 (>500mg)	0.725 (0.558-0.941)	0.016*	0.866 (0.659-1.136)	0.299
Gender (female)	0.968 (0.751-1.247)	0.802	0.951 (0.736-1.228)	0.700
BMI (>27 kg/m^2)	0.713 (0.558-0.912)	0.007*	0.690 (0.539-0.884)	0.003*
mNUTRIC score	1.378 (1.282-1.481)	<0.001*	1.371 (1.274-1.475)	<0.001*
Sepsis on admission (yes)	1.144 (0.895-1.462)	0.284	1.115 (0.867-1.433)	0.397
Admission type (surgical)	0.980 (0.751-1.279)	0.882	0.912 (0.678-1.225)	0.540
PN administered days 1-7 (yes)	1.315 (0.972-1.779)	0.076**	1.130 (0.808-1.580)	0.474

D. Duration of mechanical ventilation, length of ICU and hospital stay

	Duration of MV			ICU LOS, TDA			HOS LOS, TDA		
	β	**SE**	**p-value**	**β**	**SE**	**p-value**	**β**	**SE**	**p-value**
Propofol dose day 1-7 (>500mg)	-0.013	0.019	0.510	-0.023	0.023	0.318	-0.008	0.022	0.721
Gender (female)	-0.005	0.017	0.759	-0.038	0.020	0.060	-0.009	0.02	0.661
BMI (>27 kg/m^2)	0.009	0.017	0.608	-0.001	0.019	0.942	0.031	0.019	0.102
mNUTRIC score	0.010	0.004	0.030*	0.015	0.005	0.003*	0.031	0.005	<0.001*
Sepsis on admission (yes)	0.005	0.017	0.793	-0.003	0.020	0.897	0.015	0.020	0.439
Admission type (surgical)	0.015	0.02	0.449	0.021	0.023	0.361	0.066	0.023	0.004*
PN administered days 1-7 (yes)	0.048	0.025	0.058	0.076	0.029	0.010*	0.113	0.029	<0.001*

E. Need for a tracheostoma and discharge destination home

	Tracheostoma needed			Discharged home alive			.. corrected for days HOS		
	β	**SE**	**p-value**	**β**	**SE**	**p-value**	**β**	**SE**	**p-value**
Propofol dose day 1-7 (>500mg)	-0.081	0.209	0.699	0.546	0.206	0.008*	0.215	0.118	0.069
Gender (female)	-0.157	0.188	0.405	0.050	0.176	0.777	0.113	0.108	0.298
BMI (>27 kg/m^2)	-0.457	0.18	0.011*	-0.179	0.168	0.287	-0.016	0.105	0.880
mNUTRIC score	0.091	0.049	0.065	-0.210	0.047	<0.001*	-0.040	0.030	<0.001*
Sepsis on admission (yes)	0.061	0.187	0.744	0.172	0.175	0.325	-0.151	0.110	0.171
Admission type (surgical)	-0.125	0.211	0.554	0.149	0.201	0.458	-0.313	0.123	0.011*
PN administered days 1-7 (yes)	0.107	0.263	0.683	0.357	0.252	0.157	-0.577	0.162	<0.001*

HR = hazard ratio; 95% CI = 95% confidence interval; BMI = body mass index; mNUTRIC = modified Nutrition Risk in Critically Ill; PN = parenteral nutrition; HOS = hospital; ICU = intensive care unit; MV = mechanical ventilation; TDA = time to alive discharge (ICU n=694; HOS n=626);

** p-value < 0.05;*

P-values were assessed using Cox proportional hazards, logistic or log-transformed linear regression models where appropriate.

Multivariable analyses revealed a statistically significant difference between the two groups regarding discharge destinations. Patients who received >500mg of propofol during the first seven days of ICU admission were more likely to be discharged home than those who did not (OR 1.675, 95% CI 1.142-2.457, p=0.008; adjusted for death as a competing risk). However, this association was no longer significant when additionally adjusted for days spent in the hospital (p=0.069). No statistically significant differences were observed between the groups in other secondary endpoints of interest (all p>0.05).

Discussion

The use of propofol is common in critically ill patients requiring mechanical ventilation, but its impact on long-term outcomes has not been extensively studied. In this large retrospective study, we investigated the effects of substantial doses of propofol, defined as cumulative administration of over 500mg during the first week of ICU admission, on clinical outcomes, including 6-month mortality.

Our findings indicate no significant association between substantial propofol use and 6-month mortality or other secondary outcomes, such as duration of mechanical ventilation and need for a tracheostomy, ICU and hospital length of stay, discharge destinations, and ICU, in-hospital, and 3-month mortality when corrected for other variables relevant for these endpoints.

Our study is consistent with a recent meta-analysis by Kotani et al. studying all-cause mortality in postoperative and critically ill patients receiving propofol versus any other sedative agent [5]. In total, they included 252 RCTs (comprising 30,757 patients). They found that propofol significantly increases mortality in non-ICU patients, as they reported higher mortality rates in the propofol group versus the comparator groups (5.2% versus 4.3%; risk ratio = 1.10; 95% confidence interval 1.01-1.20; p=0.03), number needed to harm 235). However, they also found no significant difference in mortality among ICU patients receiving propofol (risk ratio = 1.04, 95% CI 0.93-1.16, p = 0.50). Of note, this meta-analysis had limitations, such as not considering the dosage and duration of propofol infusions in the analyses and including studies with varying follow-up times.

In our multivariable analyses, lower BMI and higher mNUTRIC score were significantly associated with 6-month mortality, consistent with previous studies [48-50].

Ho and colleagues conducted a meta-analysis of 16 trials among heterogeneous populations of critically ill patients, including trauma and cardiothoracic surgery, to

evaluate the association between propofol versus alternative sedatives on secondary outcomes such as length of ICU stay and duration of mechanical ventilation [51]. They reported that patients sedated with propofol might have a reduced length of mechanical ventilation and ICU LOS compared to long-acting benzodiazepines (weighted-mean difference in days -0.99, 95% CI -1.51 to -0.47, p = 0.0002). However, this association was lost when the comparison was limited to propofol and midazolam. Garcia et al.'s systematic review and meta-analysis reported similar findings, including seven RCTs evaluating clinical outcomes of critically ill ICU patients who received propofol or midazolam [52]. Conversely, Zhang and coworkers' network meta-analysis, which included 16 studies comparing propofol and midazolam, found a shorter duration of mechanical ventilation in favour of the propofol group. However, the analysis included heterogeneous study populations due to a broad definition of critical illness [53].

Several studies have compared propofol versus dexmedetomidine use with heterogeneous study populations and varying results. Heybati et al.'s most recent meta-analysis of eight studies showed no differences in the duration of mechanical ventilation, ICU LOS, and mortality in critically ill, non-cardiac surgery patients between both hypnotic agents [54]. However, no studies have investigated the associations between propofol administration and clinical outcomes that reflect ICU-AW, such as the need for a tracheostomy to wean from mechanical ventilation and discharge destinations.

Our study's findings suggest that the effect of substantial doses of propofol on mitochondrial function is limited and does not significantly affect muscle function or ICU-acquired weakness and therefore does not impact clinical outcomes. Of note, this is probably only true for the least sick patients, as we would expect clinical staff to use alternative sedatives in unstable patients. This is reflected in the baseline data: patients in the no substantial propofol dose group had higher APACHE II scores and higher mortality.

Another possible explanation is that propofol's early pharmacological suppression of mitochondrial function may facilitate an adaptive process, and discontinuation of propofol may allow for mitochondrial function recovery. However, this is speculative and more basic research is necessary to elucidate the underlying mechanisms involved.

Strengths

This study is the most extensive to date regarding the clinical outcomes of patients who received propofol during their ICU stay. Strengths of this study include an extended follow-up period of 6 months and evaluation of several outcome parameters, including the need for a tracheostomy to wean from mechanical ventilation and discharge destinations. Additionally, due to the ICU patient data management system, non-

nutritional calories could be precisely quantified, and nutritional support could be adapted to prevent overfeeding [55].

Limitations

First, it is a retrospective observational study, and there were significant baseline differences between the substantial propofol and no substantial propofol dose groups, introducing bias and confounding. In univariable analysis, there appeared to be a survival benefit for the substantial propofol dose group, mainly when administered during the late acute phase of illness, but this effect disappeared in multivariable analyses due to differences in baseline characteristics. Moreover, we might have introduced bias by defining the cut-off value to distinguish patients who were administered a substantial dose of propofol and those who were not. Additionally, the study is limited by its single-centre design and the inclusion of only critically ill patients who were mechanically ventilated for at least seven days. Furthermore, the energy targets used in the ICU were based on the static FAO/WHO/UNU formula, not accounting for individual needs measured with indirect calorimetry.

The study also had some limitations regarding propofol and other medications. Only propofol use during the first seven days was analyzed, so propofol administration during more than seven days in 252 patients might have altered outcomes. The cut-off value of 500mg of propofol was arbitrarily chosen to distinguish patients who received a substantial dose of propofol from patients who received only small doses periprocedurally. The study did not adjust for sedation intensity (depth), as measured by the RASS score. Finally, the possible effects of any other medication administered (except for muscle relaxants or chronic steroids) could not be corrected [56].

Future directions

Future research should focus on conducting randomised controlled trials to confirm the safety of the administration of substantial doses of propofol in critically ill patients and to investigate its potential association with outcomes such as ICU-acquired weakness and discharge destinations.

Conclusion

In conclusion, this retrospective observational study found no significant association between substantial propofol administration (defined as a cumulative dose >500mg during the first week of ICU admission) and adverse clinical outcomes such as mortality, duration of mechanical ventilation, need for tracheostomy, ICU and hospital length of stay, and discharge destinations. Therefore, sedation with substantial doses of propofol, guided by RASS scores and sedation interruptions, appears safe in the least sick (as evaluated by clinical staff) critically ill adult patients who require mechanical

ventilation for at least seven days. It is unlikely that propofol has a significant impact on mitochondrial function translating into negative effects on clinically relevant endpoints in these patients.

References

1. Marik PE. Propofol: therapeutic indications and side-effects. Curr Pharm Des. 2004;10(29):3639-49.
2. Marik PE. Propofol: an immunomodulating agent. Pharmacotherapy. 2005 May;25(5):28S-33S.
3. Ho KM, Ng JY. The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. Intensive Care Med. 2008 Nov;34(11):1969-79.
4. Devlin JW, Roberts RJ. Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. Anesthesiol Clin. 2011 Dec;29(4):567-85.
5. Kotani Y, Pruna A, Turi S, Borghi G, Lee TC, Zangrillo A, Landoni G, Pasin L. Propofol and survival: an updated meta-analysis of randomised clinical trials. Crit Care. 2023 Apr 12;27(1):139.
6. Zhou Y, Jin X, Kang Y, Liang G, Liu T, Deng N. Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: a prospective, randomised study. Crit Care. 2014 Jun;18(3):R122.
7. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM. Propofol infusion syndrome in adults: a clinical update. Crit Care Res Pract. 2015;2015:260385.
8. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia. 2007 Jul;62(7):690-701.
9. Sumi C, Okamoto A, Tanaka H, Nishi K, Kusunoki M, Shoji T, Uba T, Matsuo Y, Adachi T, Hayashi JI, Takenaga K, Hirota K. Propofol induces a metabolic switch to glycolysis and cell death in a mitochondrial electron transport chain-dependent manner. PLoS One. 2018 Feb;13(2):e0192796.
10. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. Br J Anaesth. 2019 Apr;122(4):448-459.
11. Li WK, Chen XJC, Altshuler D, Islam S, Spiegler P, Emerson L, Bender M. The incidence of propofol infusion syndrome in critically-ill patients. J Crit Care. 2022 Oct;71:154098.
12. Krajčová A, Løvsletten NG, Waldauf P, Frič V, Elkalaf M, Urban T, Anděl M, Trnka J, Thoresen GH, Duška F. Effects of Propofol on Cellular Bioenergetics in Human Skeletal Muscle Cells. Crit Care Med. 2018 Mar;46(3):e206-e212.
13. Diedrich DA, Brown DR. Analytic reviews: propofol infusion syndrome in the ICU. J Intensive Care Med. 2011 Mar-Apr;26(2):59-72.
14. Vanlander AV, Okun JG, de Jaeger A, Smet J, De Latter E, De Paepe B, Dacremont G, Wuyts B, Vanheel B, De Paepe P, Jorens PG, Van Regenmortel N, Van Coster R. Possible pathogenic mechanism of propofol infusion syndrome involves coenzyme q. Anesthesiology. 2015 Feb;122(2):343-52.
15. Finsterer J, Frank M. Propofol Is Mitochondrion-Toxic and May Unmask a Mitochondrial Disorder. J Child Neurol. 2016 Nov;31(13):1489-1494.
16. Supinski GS, Schroder EA, Callahan LA. Mitochondria and Critical Illness. Chest. 2020 Feb;157(2):310-322.
17. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002 Jul;360(9328):219-23.
18. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence. 2014 Jan;5(1):66-72.

19. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. Biochim Biophys Acta Mol Basis Dis. 2017 Oct;1863(10 Pt B):2534-2545.
20. Garrabou G, Morén C, López S, Tobías E, Cardellach F, Miró O, Casademont J. The effects of sepsis on mitochondria. J Infect Dis. 2012 Feb;205(3):392-400.
21. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, Larsson L. The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. Physiol Rev. 2015 Jul;95(3):1025-109.
22. McClave SA, Wischmeyer PE, Miller KR, van Zanten ARH. Mitochondrial Dysfunction in Critical Illness: Implications for Nutritional Therapy. Curr Nutr Rep. 2019 Dec;8(4):363-373.
23. Brealey D, Karyampudi S, Jacques TS, Novelli M, Stidwill R, Taylor V, Smolenski RT, Singer M. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. Am J Physiol Regul Integr Comp Physiol. 2004 Mar;286(3):R491-7.
24. Jiroutková K, Krajčová A, Ziak J, Fric M, Waldauf P, Džupa V, Gojda J, Němcova-Fürstová V, Kovář J, Elkalaf M, Trnka J, Duška F. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. Crit Care. 2015 Dec;19:448.
25. Owen AM, Patel SP, Smith JD, Balasuriya BK, Mori SF, Hawk GS, Stromberg AJ, Kuriyama N, Kaneki M, Rabchevsky AG, Butterfield TA, Esser KA, Peterson CA, Starr ME, Saito H. Chronic muscle weakness and mitochondrial dysfunction in the absence of sustained atrophy in a preclinical sepsis model. Elife. 2019 Dec;8:e49920.
26. Branca D, Roberti MS, Lorenzin P, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol on the oxidative phosphorylation of isolated rat liver mitochondria. Biochem Pharmacol. 1991 June 21st;42(1):87-90.
27. Branca D, Roberti MS, Vincenti E, Scutari G. Uncoupling effect of the general anesthetic 2,6-diisopropylphenol in isolated rat liver mitochondria. Arch Biochem Biophys. 1991 Nov 1;290(2):517-21.
28. Branca D, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol (propofol) on isolated rat heart mitochondria. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 1995 Jan;110(1):41-5.
29. Rigoulet M, Devin A, Avéret N, Vandais B, Guérin B. Mechanisms of inhibition and uncoupling of respiration in isolated rat liver mitochondria by the general anesthetic 2,6-diisopropylphenol. Eur J Biochem. 1996 Oct 1;241(1):280-5.
30. Fedorov A, Lehto A, Klein J. Inhibition of mitochondrial respiration by general anesthetic drugs. Naunyn Schmiedebergs Arch Pharmacol. 2023 Feb;396(2):375-381.
31. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care. 2015 Aug;19(1):274.
32. Moonen HPFX, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: consequences for nutrition therapy. Curr Opin Crit Care. 2020 Aug;26(4):346-354.
33. Abdelmalik PA, Rakocevic G. Propofol as a Risk Factor for ICU-Acquired Weakness in Septic Patients with Acute Respiratory Failure. Can J Neurol Sci. 2017 May;44(3):295-303.
34. Lönnqvist PA, Bell M, Karlsson T, Wiklund L, Höglund AS, Larsson L. Does prolonged propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? Br J Anaesth. 2020 Sep;125(3):e334-e336.
35. Zorrilla-Vaca A, Arevalo JJ, Escandón-Vargas K, Soltanifar D, Mirski MA. Infectious Disease Risk Associated with Contaminated Propofol Anesthesia, 1989-2014(1). Emerg Infect Dis. 2016 Jun;22(6):981-92.

36. Tsuchiya M, Asada A, Maeda K, Ueda Y, Sato EF, Shindo M, Inoue M. Propofol versus midazolam regarding their antioxidant activities. Am J Respir Crit Care Med. 2001 Jan;163(1):26-31.
37. Tsuchiya H, Ueno T, Tanaka T, Matsuura N, Mizogami M. Comparative study on determination of antioxidant and membrane activities of propofol and its related compounds. Eur J Pharm Sci. 2010 Jan 31;39(1-3):97-102.
38. Marik PE. Propofol: an immunomodulating agent. Pharmacotherapy. 2005 May;25(5 Pt 2):28S-33S.
39. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study. JPEN J Parenter Enteral Nutr. 2016 Jan;40(1):45-51.
40. Weijs PJ, Wischmeyer PE. Optimising energy and protein balance in the ICU. Curr Opin Clin Nutr Metab Care. 2013 Mar;16(2):194-201.
41. Koekkoek WACK, van Setten CHC, Olthof LE, Kars JCNH, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study. Clin Nutr. 2019 Apr;38(2):883-890.
42. Lambell KJ, Tatucu-Babet OA, Chapple LA, Gantner D, Ridley EJ. Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care. 2020 Feb;24(1):35.
43. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014 Dec;18(6):701.
44. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, Perner A, Kondrup J. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012 Aug;31(4):462-8.
45. Tsai JR, Chang WT, Sheu CC, Wu YJ, Sheu YH, Liu PL, Ker CG, Huang MC. Inadequate energy delivery during early critical illness correlates with increased risk of mortality in patients who survive at least seven days: a retrospective study. Clin Nutr. 2011 Apr;30(2):209-14.
46. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care. 2019 Nov;23(1):368.
47. FAO/WHO/UNU Expert Consultation. Equations for the prediction of basal metabolic rate. In: Energy and protein requirements. FAO/WHO/UNU. 1985. http://www.fao.org/3/aa040e/AA040E15.htm. [Accessed April 18, 2023].
48. Zhao Y, Li Z, Yang T, Wang M, Xi X. Is body mass index associated with outcomes of mechanically ventilated adult patients in intensive critical units? A systematic review and meta-analysis. PLoS One. 2018 Jun 8;13(6):e0198669.
49. O'Brien JM Jr, Philips GS, Ali NA, Aberegg SK, Marsh CB, Lemeshow S. The association between body mass index, processes of care, and outcomes from mechanical ventilation: a prospective cohort study. Crit Care Med. 2012 May;40(5):1456-63.
50. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15(6):R268.
51. Ho KM, Ng JY. The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. Intensive Care Med. 2008 Nov;34(11):1969-79.
52. Garcia R, Salluh JIF, Andrade TR, Farah D, da Silva PSL, Bastos DF, Fonseca MCM. A systematic review and meta-analysis of propofol versus midazolam sedation in adult intensive care (ICU) patients. J Crit Care. 2021 Aug;64:91-99.

53. Zhang Z, Chen K, Ni H, Zhang X, Fan H. Sedation of mechanically ventilated adults in intensive care unit: a network meta-analysis. Sci Rep. 2017 Mar;7:44979.
54. Heybati K, Zhou F, Ali S, Deng J, Mohananey D, Villablanca P, Ramakrishna H. Outcomes of dexmedetomidine versus propofol sedation in critically ill adults requiring mechanical ventilation: a systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2022 Oct;129(4):515-526.
55. Bousie E, van Blokland D, Lammers HJ, van Zanten AR. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr. 2016 Dec;70(12):1443-1450.
56. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, Khoo TM, Ali SB, Saman MA, Shaltut A, Tan CC, Yong CY, Bailey M; Sedation Practice in Intensive Care Evaluation (SPICE) Study Group investigators. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med. 2013 May;39(5):910-8.

Supplemental material

Supplement 1. Target calculations (energy / protein)

A. Energy targets

Resting energy expenditure (REE)

Male	
18-30y	15.4 x weight - 27 x length + 717
30-60y	11.3 x weight - 16 x length + 901
>60y	8.8 x weight + 1128 x length - 1071

Female	
18-30y	13.3 x weight + 334 x length + 35
30-60y	8.7 x weight - 25 x length + 865
>60y	9.2 x weight + 637 x length - 302

Adaptation to ICU patient

Pressure control ventilation	
BMI ≤ 27	REE + 20%
BMI 27-30	REE + 20% (weight corrected to BMI 27)
BMI ≥ 30	60-70% of REE + 20% (weight corrected to BMI 27)

Pressure support ventilation	
BMI ≤ 27	REE + 30%
BMI 27-30	REE + 30% (weight corrected to BMI 27)
BMI ≥ 30	60-70% of REE + 30% (weight corrected to BMI 27)

B. Protein targets

BMI ≤ 27	1.5 g/kg of actual body weight
BMI 27-30	1.5 g/kg, weight corrected to BMI 27
BMI 30-40	2.0 g/kg ideal body weight (male BMI 22.5; female BMI 21)
BMI ≥ 40	2.5 g/kg ideal body weight (male BMI 22.5; female BMI 21)

y = years; weight in kilograms; length in meters;
ICU = Intensive care unit; BMI = Body mass index; REE = Resting energy expenditure.

Supplement 2. Nutritional parameters (days 1-7 after ICU admission)

			Cumulative propofol dose day 1-7		
		All patients	**≤500mg**	**>500mg**	**p-value[a)]**
		(n=839)	***(n=221)***	***(n=618)***	
Hours until start nutrition	*median [IQR]*	6.6 [3.4-17.2]	6.1 [3.1-15.1]	6.8 [3.5-18.0]	0.180
PN administered (yes)	*n (%)*	142 (16.9)	51 (23.1)	91 (14.7)	0.004*
Energy target (kcal/kg IBW*day)[b)]	*median [IQR]*	24.9 [18.4-26.7]	24.9 [18.9-26.7]	24.9 [18.3-26.7]	0.887
Energy intake (kcal/kg IBW*day)	*mean (SD)*	17.8 (5.3)	17.9 (5.3)	17.8 (5.3)	0.987
Nutritional	*mean (SD)*	15.0 (5.5)	16.2 (5.3)	14.5 (5.5)	<0.001*
Non-nutritional	*median [IQR]*	2.2 [1.2-4.1]	1.1 [0.6-2.2]	2.6 [1.5-4.4]	<0.001*
Propofol derived	*median [IQR]*	0.7 [0.1-2.1]	0 [0]	1.2 [0.5-2.7]	<0.001*
Glucose derived	*median [IQR]*	0.7 [0.3-1.2]	0.8 [0.3-1.3]	0.7 [0.3-1.2]	0.419
Citrate derived	*median [IQR]*	0 [0]	0 [0]	0 [0]	0.987
% Non-nutritional calories	*median [IQR]*	13.1 [6.7-25.0]	7.1 [2.9-13.3]	16.0 [9.0-28.2]	<0.001*
Adequacy to target day 1-7 (%)	*mean (SD)*	93.5 (26.1)	93.8 (27.4)	93.4 (25.7)	0.830
Adequacy to target day 1-3 (%)	*mean (SD)*	87.2 (40.8)	86.7 (42.4)	87.3 (40.2)	0.923
Adequacy to target day 4-7 (%)	*mean (SD)*	96.2 (25.4)	96.6 (26.3)	96.1 (25.1)	0.793
Protein target (g/kg IBW*day)[b	*median [IQR]*	1.5 [1.5-1.6]	1.5 [1.5-1.6]	1.5 [1.5-1.6]	0.140
Protein intake (g/kg IBW*day)	*mean (SD)*	0.92 (0.3)	0.97 (0.3)	0.90 (0.3)	0.007*
Adequacy to target day 1-7 (%)	*mean (SD)*	73.7 (23.7)	78.3 (24.0)	72.0 (23.4)	0.004*
Adequacy to target day 1-3 (%)	*mean (SD)*	59.3 (39.7)	67.7 (41.3)	56.3 (38.7)	<0.001*
Adequacy to target day 4-7 (%)	*mean (SD)*	79.6 (22.8)	82.5 (23.3)	78.6 (22.6)	0.030*

IQR = interquartile range; n = number of patients; SD = standard deviation; PN = parenteral nutrition; IBW = ideal body weight;

[a)] p-values were calculated using the chi-square test, independent samples t-test or wilcoxon rank sum test where appropriate;

[b)] during the first 3 days, energy and protein targets are gradually increased (in daily steps of 25%) to full target on day 4

** p-value <0.05.*

Supplement 3. Univariable and multivariable COX regressions for the association of early (day 1-3) versus late (day 4-7) propofol administration and the primary endpoint of 6-month mortality

A. Cumulative propofol dose day 1-3

	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Propofol dose day 1-3 (>500mg)	0.793 (0.595-1.059)	0.116	0.961 (0.713-1.295)	0.793
Gender (female)	0.905 (0.705-1.161)	0.431	1.116 (0.868-1.435)	0.392
BMI (>27 kg/m^2)	0.733 (0.577-0.930)	0.011*	0.711 (0.559-0.903)	0.005*
mNUTRIC score	1.386 (1.291-1.487)	<0.001*	1.383 (1.288-1.485)	<0.001*
Sepsis on admission (yes)	1.142 (0.899-1.451)	0.276	1.138 (0.891-1.454)	0.301
Admission type (surgical)	0.996 (0.769-1.291)	0.976	0.897 (0.674-1.195)	0.459
PN administered day 1-7 (yes)	1.355 (1.012-1.815)	0.041*	1.175 (0.850-1.625)	0.328

B. Cumulative propofol dose day 4-7

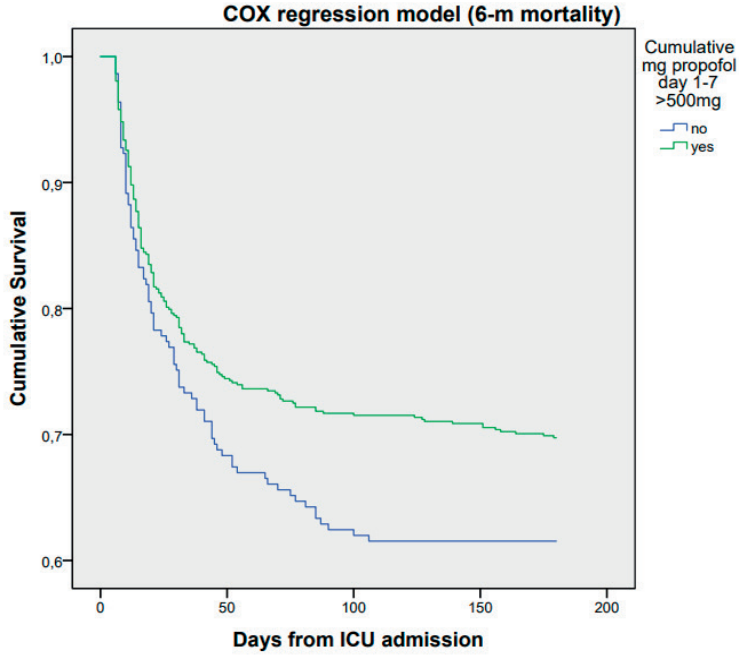
	Univariable		Multivariable	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Propofol dose day 4-7 (>500mg)	0.750 (0.591-0.952)	0.018*	0.967 (0.750-1.247)	0.796
Gender (female)	0.905 (0.705-1.161)	0.431	0.897 (0.698-1.152)	0.394
BMI (>27 kg/m^2)	0.733 (0.577-0.930)	0.011*	0.711 (0.559-0.904)	0.005*
mNUTRIC score	1.386 (1.291-1.487)	<0.001*	1.382 (1.285-1.486)	<0.001*
Sepsis on admission (yes)	1.142 (0.899-1.451)	0.276	1.137 (0.889-1.455)	0.306
Admission type (surgical)	0.996 (0.769-1.291)	0.976	0.895 (0.671-1.193)	0.449
PN administered day 1-7 (yes)	1.355 (1.012-1.815)	0.041*	1.176 (0.850-1.626)	0.328

HR = hazard ratio; 95% CI = 95% confidence interval; BMI = Body mass index; mNUTRIC = modified Nutrition Risk in Critically Ill; PN = parenteral nutrition;
** p-value < 0.05;*
Multivariable Cox regression analyses were conducted using the Enter and Forward (Stepwise Wald) methods.

Supplement 4. Final multivariable model for the association of propofol administration during the first week of ICU admission and the primary endpoint of 6-month mortality

Cumulative propofol dose day 1-7	6-month mortality (%)	hazard ratio (95% CI)
≤500mg	85 (38.5)	1
>500mg	187 (30.3)	0.753 (0.582-0.973)

Univariable predictors (p<0.01)	propofoldose day 1-7, BMI, mNUTRIC, PN administered day 1-7
Model 1 (enter method)	BMI, mNUTRIC
Model 2 (stepwise forward)	BMI, mNUTRIC
Final multivariable model	BMI, mNUTRIC



95% CI = 95% confidence interval; BMI = Body mass index; mNUTRIC = modified Nutrition Risk in Critically Ill; PN = parenteral nutrition.

CHAPTER 9

9

General Discussion

The survival rates of intensive care unit (ICU) patients are steadily increasing over the past decades. However, little is known about long-term outcomes. A decrease in quality of life (QoL) has been reported as many ICU survivors suffer from prolonged physical, mental and cognitive problems. Even for post-ICU patients not experiencing these issues, (complete) recovery may take an unexpectedly long time. Until now, there are minimal evidence-based therapies to enhance recovery and thus optimise long-term health. Undoubtedly, recovery after the acute phase of critical illness cannot be accomplished without adequate nutrition. However, the disrupted metabolism (including mitochondrial dysfunction) has implications for nutrition therapy during the several (metabolic) phases of critical illness. Nevertheless, formal guidelines for the dynamic nutritional targets of (particularly post-)ICU patients still need to be developed. Therefore, this thesis aimed to increase knowledge about the nutritional journey of critically ill patients in the ICU (parts 1 and 3: chapters 2-5 and 7-8) and convalescence (part 2: chapter 6), with the ultimate goal to improve current nutritional strategies and prevent adverse effects.

In this chapter, the main findings of this thesis are summarized briefly first. Secondly, the results are discussed in more detail and in the perspective of current literature. In addition, clinical implications and challenges are provided. Thirdly, the methodological issues of the studies included in this thesis are addressed. Finally, suggestions for future research are proposed.

9.1 Main findings

We found that a novel, more user-friendly mechanical support device equipped with indirect calorimetry functionalities was accurate in determining resting energy expenditure in mechanically ventilated critically ill patients (compared to the current gold standard) (**Chapter 2**). In contrast, there was a poor correlation between indirect calorimetry and several predictive equations. **Chapter 3** demonstrated that real-time video-assisted placement of upper gastrointestinal feeding tubes was highly successful for gastric placement. However, deep jejunal placement was achieved in only a low number of attempts. The technique was safe in avoiding tracheal malpositioning. **Chapter 4** provided a literature review of recent findings concerning refeeding hypophosphatemia (RH) in critically ill patients, including recommendations for daily practice. In **Chapter 5**, we found that high protein - not carbohydrate or lipid - intake during the first three days of ICU admission in patients with RH was associated with increased 6-month mortality, but not short-term outcomes. In **Chapter 6** we demonstrated that most patients recovering from critical illness did not reach their energy and protein targets in the post-ICU convalescence. However,

this was highly dependent on the nutritional route, and was lowest among patients with oral nutrition only (despite of food fortification strategies and/or oral nutritional supplements). Additionally, the ordered amount of food failed to meet the predicted targets. Conversely, the best intake was seen in patients with (supplemental) enteral nutrition (EN). Nonetheless, discontinuation of EN posed a nutritional risk, resulting in immediate and sustained drops of energy and protein intake. In **Chapters 7** and **8** we studied the evolution of mitochondrial dysfunction during sepsis, as well as the impact of continuous sedation (which in vivo suppresses mitochondrial function) on clinical outcomes, as this has consequences for nutritional support. We found a higher basal and ATP-linked respiration in peripheral blood mononuclear cells (PBMCs) within the first week of ICU admission in septic patients compared to healthy matched controls (**Chapter 7**). In addition, a progressive increase of basal and ATP-linked mitochondrial respiration was negatively associated with 3-month mortality. Regarding the impact of continuous sedation during the first week of ICU stay, no significant association between substantial propofol administration and adverse clinical outcomes was demonstrated (**Chapter 8**).

A detailed discussion of the main findings of this thesis in the context of current literature is provided below.

9.2 Main findings in perspective, clinical implications, and challenges

9.2.1 Estimating energy requirements

Critically ill patients admitted to an Intensive care unit (ICU) should receive nutritional support matched to their metabolic needs (1–4). Both under- and overfeeding are associated with increased morbidity and mortality (1–3,5–7). However, critical illness significantly affects metabolism. During the acute phase, there is a significant increase in endogenous energy production while metabolic demands are reduced, resembling a hibernation-like state or bioenergetic downregulation (8–13). Conversely, in the chronic or recovery phase, patients' metabolic needs increase drastically and may exceed the guideline-recommended energy and protein intake in this period, although formal guidelines are lacking (14,15). Moreover, energy expenditure (EE) varies during critical illness and is influenced by the patients' condition (sepsis, trauma) and medication administered (vasopressors, sedation, analgesics or neuromuscular blocking agents) (16–19). Predictive equations – such as the Harris-Benedict equation – are population-based averages, have lower accuracy rates than indirect calorimetry, and are unreliable in predicting EE in individual patients, as can be concluded from **Chapter 2** and earlier work (3,20–22). Therefore, the recent European Society for Clinical Nutrition

and Metabolism (ESPEN) adult ICU guideline recommends indirect calorimetry (IC) to estimate EE during critical illness to guide optimal individual nutritional support (4). However, IC is unavailable in many hospitals due to costs or user difficulties, such as time-consuming calibration procedures (23,24).

Easy-to-use novel bedside systems with modern and intuitive interfaces, such as the Beacon Care system (Mermaid Care Company, Denmark), may overcome the aforementioned problem. This device has proven its reliability in both healthy individuals and, in our study, mechanically ventilated ICU patients (25). In **Chapter 2** we reported a mean underestimation in calculated REE of only -96.2 kcal/day (4.5%) compared to the gold standard at that time in our ICU (Quark RMR, Cosmed, Rome, Italy). There was low bias and good reliability. In contrast, there was a poor correlation (<0.40) between the separate indirect calorimetry devices and several predictive equations. Therefore, predictive equations should not be used to estimate dynamic individual metabolic demands. Instead, we promote large-scale use of IC to measure REE to optimise nutritional support. Ideally, IC measurements are repeated every two to three days and after significant changes in clinical conditions or treatments, such as new infections or significant changes in doses of sedative medication (24,26).

Feasibility of indirect calorimetry

However, IC is not always feasible or reliable due to the sensitivity of measurements in ICU patients (7). To ensure a reliable, valid, and representative assessment of REE in our study, subjects were prohibited from engaging in any physical activity, such as physiotherapy, and from experiencing changes in ventilatory support, except for alterations in the fraction of inspired oxygen (FiO_2), for two hours prior to the measurements. Furthermore, no inhalation drugs were administered during actual measurements. Finally, patients with high levels of mechanical ventilatory support (*i.e.,* FiO_2 >0.6 or positive end-expiratory pressure >12 cmH_2O), ventilated in the prone position, or with unspecified amounts of air leakage (such as uncuffed tracheostomy cannula, endotracheal tube cuff leaks, tracheoesophageal fistulae, subcutaneous emphysema, or chest tube drainage) or a body temperature making an accurate measurement impossible (<36 or >42 degrees Celsius) were excluded. Even minor disturbances, including patients' unrest or anxiety, ultimately increase energy expenditure, as is reflected in the large standard deviations (and wide 95% confidence intervals) reported. In addition, we excluded all patients receiving any form of renal replacement therapy as this was thought to influence REE (27). However, more recently, Jonckheer and colleagues demonstrated that IC measurements during continuous veno-venous hemofiltration are feasible and reliable without a correction factor (28).

Regarding post-ICU convalescence, Rousseau *et al.* demonstrated that frequently used predictive equations are inaccurate in predicting energy expenditure in this period (29). EE was measured with indirect calorimetry and was significantly lower. Therefore, IC measurements are preferably continued in the post-ICU period. However several factors may hamper this, such as the unavailability of devices, lack of trained personnel, competing work priorities, and measurement limitations, such as oxygen therapy in non-ventilated patients (7). Measuring REE in awake patients using a canopy hood may also be challenging due to claustrophobia. Again, the optimal frequency of measurements to adapt nutritional support in the post-ICU phase is unknown, with an acceptable measurement burden for the patient. As mentioned above, Oshima *et al.* suggest repeating IC every 2-3 days during ICU stay, but no recommendations are available for the post-ICU convalescence phase (24).

9.2.2 Safe tube feeding

Once REE has been estimated and energy targets are set, critically ill patients often require nasogastric or -jejunal access for enteral nutrition because they cannot have oral intake. The European, American, and Canadian clinical nutrition guidelines recommend gastric access as the standard approach (4,30,31). Post-pyloric access, with post-ligament of Treitz as the optimal position, is recommended in patients with a high risk of aspiration or in case of persistent gastric feeding intolerance despite the administration of prokinetics (4,31,32).

To identify pulmonary misplacement, as nasogastric (NG) feeding tubes are typically inserted blindly, X-ray is necessary to ensure the correct positioning before initiating nutritional therapy. This results in radiation exposure and additional costs for each NG/NJ insertion and is not foolproof (33–38). Nasojejunal (NJ) feeding tube placement is typically performed using Cortrak or endoscopic guidance (34,39–41). These methods have disadvantages, such as delayed nutritional delivery due to the limited availability of qualified operators and equipment. The placement of feeding tubes under direct visualisation of anatomical landmarks using Integrated Real-Time Imaging System (IRIS) technology has been suggested as an alternative technique.

Feeding tube placement using IRIS technology

In **Chapter 3**, real-time video-assisted nasogastric placement using IRIS technology was highly successful (96.8%), similar to previous reports (42,43). Therefore, it is a suitable alternative method for blind insertion in ICU patients as immediate detection of tracheal placement and low rates of adverse events were encountered (42–46).

Furthermore, X-ray confirmation is no longer necessary when gastric placement is the goal since there was 100% agreement between X-ray and real-time imaging regarding

its position in the stomach, similar to previous results (44,45). This advantage over the current blind insertion methods includes the possibility to commence nutritional support immediately after insertion and no (additional) radiation dose (47). Hemington-Gorse *et al.* calculated that a chest or abdominal film dose is similar to 10 days or 2-3 years of background radiation, respectively (47). ICU patients often require multiple radiological investigations, so any exposure reduction benefits the patient.

However, the IRIS technology is currently *un*suitable for post-pyloric (*i.e.,* the tube tip past the pylorus) and particularly nasojejunal (*i.e.,* the tube tip past the ligament of Treitz) positioning. We reported a 75% and 7% success rate, respectively, similar to results reported in literature (42,45,48). This is in contrast with current methods (Cortrak and endoscopy), which have success rates of 82.6-85% and 83.1-89%, respectively (40,49,50).

The disappointing results in our study were mainly due to a lack of anatomical markers on the exact position in the duodenum and the tube's flexibility, hampering the passing of the tube to a deep post-pyloric position. Moreover, many critically ill ICU patients have reduced gastric motility and suffer from retroperistalsis, further hampering post-pyloric tube positioning (32). In our study, only one (out of four; 25%) post-pyloric feeding tube insertion procedure was successful in patients with delayed gastric emptying (defined as gastric residual volume >500mL/24h). In patients who were administered prokinetics, this was 75% (n=3).

Promising features

Nonetheless, real-time video-assisted tube insertion has promising features. When the IRIS technology could be improved to be more suitable for post-pyloric placement, there is no need to exclude patients with medical implants affected by electromagnetic fields, as is necessary with the Cortrak technique (51). Compared to endoscopic procedures, IRIS-guided placement can be performed with less sedation. In our study, only a third of conscious participants were administered midazolam periprocedural. Moreover, IRIS-guided insertion may avoid time-consuming scheduling with different departments and – in some hospitals – removes the risk associated with transporting critically ill patients through the hospital (52,53). The device necessitates a modest amount of training, enabling a larger group of physicians to perform the procedure. Taylor and coworkers recently demonstrated that novice, non-endoscopist operators merely trained using an operator guide can also interpret the IRIS tube's position accurately (46).

In our study, IRIS feeding tubes were promptly inserted whenever the study team was available, eliminating the need to wait for an endoscopy team. This protocol resulted in a reduction in procedure time and alleviated the demand for personnel. Placement

of Cortrak and endoscopic feeding tubes during weekends and holidays is challenging. Frequently, patients who need these interventions must wait until the next working day, which causes considerable feeding delays. Delays of up to 7.5 hours until initiation of feeding translate into a mean caloric deficit of 850 kilocalories (52,54). After initial electromagnetically guided placement fails, this delay may increase to an average of 17 hours before a feeding tube is inserted endoscopically or radiologically (52). Although not investigated in this study, similar delays with the IRIS technology could be expected. However, the time until the first attempt was much shorter than seven hours in our study.

Finally, IRIS technology has two additional potential advantages over the pre-existing technologies:

- If migration of the feeding tube is suspected, its position can be checked at the bedside, omitting the need for additional X-ray (42,44). Moreover, it is possible to rewire and reposition the tube, like Cortrak tubes. In contrast, endoscopically placed tubes that migrate would necessitate the removal of the tube and replacement in a new procedure (including the need for sedation) (50).
- A cost reduction is hypothesised. Although conventional post-pyloric feeding tubes are less expensive, additional costs are incurred for (repeated) radiography. Compared to gastro-endoscopy, IRIS-guided insertion reduces console and staffing workload costs, including the gastro-endoscopy team and hospital patient transporters.

9.2.3 Metabolic derangements during (re)feeding

The reintroduction of macronutrients after a period of significant malnutrition might induce refeeding syndrome (RFS) in patients at risk, which is hallmarked by refeeding hypophosphatemia (RH) as described in the literature review in **Chapter 4**. Previous studies demonstrated a survival benefit in patients who receive caloric restriction for at least 48 hours (55,56). However, all current literature addresses the total energy provision but not specific macronutrients. To our knowledge, we were the first to investigate this in this patient group. In **Chapter 5** we found a significant association between 6-month mortality and protein intake of RH patients during days 1-3 of ICU admission in multivariable models, favouring the low intake group (≤0.71 g/kg*day; hazard ratio (HR) 2.224, 95% confidence interval (95% CI) 1.261-3.923, p=0.006). These findings are similar to those reported by Koekkoek and colleagues in the general ICU population (not specifically RH patients) (57). They demonstrated a time-dependent effect of protein intake with the lowest 6-month mortality observed in the patient group with low protein provision (*i.e.* <0.8 g/kg*day; HR for >0.8 g/kg*day: 1.231, 95% CI, 1.040-1.457, p=0.016) during the early acute phase (day 1-3), and intermediate protein administration (i.e. 0.8-1.2 g/kg*day; HR 0.716, 95% CI 0.558-0.917, p=0.008) during the late acute phase (day 4-7). Our and Koekkoek's findings regarding the association

between protein intake and mortality contrast with a recent systematic review and meta-analysis by Lee *et al.*, including 23 randomised controlled trials (RCTs), adding up to 3,303 patients (58). In this large study, the effect of lower (defined as pooled mean 0.92±0.30 g/kg*day) and higher (1.49±0.48 g/kg*day; mean difference 0.49 g/kg*day, 95% CI 0.37-0.61, p<0.00001) protein provision with similar daily energy delivery were compared on clinical outcomes of critically ill patients. Except for the patient subgroup with acute kidney injury in which higher protein provision was associated with increased mortality (RR 1.42, 95% CI 1.11-1.82, p=0.005; I^2=0%), neither differences in overall mortality, nor infectious complications, ICU- and hospital length of stay, discharge destinations and muscle strength were observed. Of note, the duration of the study period varied between 3 to 28 days, not making a distinction between the early acute (days 1-3) and late acute (days 4-7) phases as Koekkoek *et al.* did, which may explain these different findings. Studies investigating protein intake in the early and late phases of critical illness, such as Bendavid and coworkers and Weijs *et al.* report divergent results, mainly due to population heterogeneity and varying cutoffs of energy and protein intake (59–61).

Until now, precise explanatory mechanisms are lacking for the time-dependent and dose-response association of protein intake and clinical outcomes in critically ill patients, as reported in **Chapter 5**. During the acute phase of critical illness, patients are highly catabolic. This results in a high protein turnover to provide energy and enhanced synthesis of acute-phase response proteins, whereas skeletal muscle protein synthesis may be decreased (57,62,63). However, in later phases of critical illness, amino acids are essential for protein synthesis and are involved in immune function to support recovery (57,64). Additional protein supplementation in the early acute phase may inhibit or result in dysfunctional autophagy, leading to increased cell damage and loss of organ function (65,66). Another explanation may be that more protein provision during the early phase may increase the oxidative burden (65). Thirdly, early mitochondrial dysfunction leads to energy deficits, inducing proteostatic effects. In this phase, protein administration may lead to enhanced muscle wasting and hepatic protein breakdown in patients with elevated glucagon levels (63,67). Finally, anabolic resistance to ingested proteins contributes to reduced muscle protein synthesis, resulting in an persistent rapid muscle breakdown, although the total amount of amino acids absorbed in the gastrointestinal tract is proven to be quite similar in critically ill compared to healthy controls (68,69). Anabolic resistance may be reflected by an increased urea-to-creatinine ratio (UCR) (70). This simple and routinely-available marker, indicating catabolism, may be used to detect prolonged critical illness (71,72). Serum creatinine levels, which serve as the denominator, are considered a surrogate measure for muscle mass. A decrease in muscle protein synthesis leads to lower serum creatinine levels. Furthermore, exogenous amino acids not utilised for protein synthesis can increase urea production, which constitutes

the numerator. A higher UCR (urea-to-creatinine ratio) has been correlated with an elevated mortality rate (HR 2.15; 95% CI 1.66-2.82) (70).

Strikingly, we found no associations between protein intake and short-term outcomes, such as ICU- or three-month mortality. These findings contrast with Koekkoek and colleagues, who demonstrated an association between time-dependent protein intake and ICU and hospital mortality, favouring the group with restricted protein intake during the first three days (57). It remains unclear why higher protein intake in the early acute phase is associated with increased long-term mortality (*i.e.*, at six months) but not with short-term outcomes in our study. The most plausible explanation is that we did not account for additional confounding factors (residual confounding), as will be discussed in 8.2 *Methodological considerations*. In addition, we speculate that this might be partly due to the higher hospital and ICU readmission rates observed in the higher protein group compared to the patients who receive fewer proteins during the first 72 hours of ICU admission (41.7 versus 42.4% and 6.7 versus 5.1%), suggesting that these patients may survive their ICU and hospital admission, but have worse recovery and are more likely to be readmitted with poor outcomes.

Our findings may have consequences for guidelines on critical care nutrition and future research. When refeeding hypophosphatemia is encountered in critical illness, caloric restriction is warranted for some days as recommended by the ESPEN guidelines (4). However, some clinicians try to preserve protein intake by supplementation during restriction for apparent reasons. Nonetheless, our data suggest that protein intake should also be restricted during this phase - thus, no supplementation should be provided.

9.2.4 Nutrition in the post-ICU phase

The nutritional journey of patients does not end at ICU discharge. In the (post-ICU) recovery period from critical illness, patients are expected to return to oral nutrition gradually. This transition is often combined with supplemental enteral or parenteral nutrition (EN; PN). Furthermore, food fortification strategies such as energy- and protein-enriched foods or oral nutrition supplements (ONS) are frequently used. Nevertheless, formal guidelines for the dynamic nutritional targets of post-ICU patients still need to be developed. Guidelines that may suit these patients recommend a caloric intake of 25-30 kcal/kg*day and a protein intake of about 1.5g/kg*day (73,74). However, during the recovery phase of critical illness, patients' metabolic targets and physical mobility increase significantly (15). Their energy expenditure will likely exceed the recommended energy and protein intake. Inadequate nutrition in this phase will lead to poor recovery (75). Therefore, optimising protein and energy intake is essential to attenuate further

loss of lean body mass and promote recovery of physical functioning and quality of life (14,76,77).

However, in **Chapter 6,** we demonstrated that most patients recovering from critical illness do not reach their energy and protein targets in post-ICU convalescence. Mean overall energy and protein intake for all nutritional groups was 24.7 kcal/kg IBW*day and 1.25 g/kg IBW*day, respectively, corresponding to 82% and 83% of targets. Only 51.2% of patients reached >90% of prescribed protein targets during their post-ICU ward stay. We report higher adequacies than current literature in which energy and protein adequacies vary between 64-81% and 46-77%, respectively (78–82). This may be due to differences in patient population, the predominant type of intake (oral and/or EN), target calculations, assessment of nutritional intake (food record charts and patient recall) and days studied. In our study, intake was measured daily (and before and after discontinuation of EN) in contrast with previous studies (78–80). Furthermore, all data on in-between meals ordered were recorded, which is not available in other studies (78). Finally, recall bias was eliminated as oral nutrition was objectively quantified through pre- and post-meal pictures and assessed by two researchers independently after completing study participation, contrasting with the studies mentioned above (79,83).

Dependent on the nutritional route

Nonetheless, the achievement of targets highly depended on the nutritional route in all studies. It was the lowest among patients with oral nutrition despite food fortification strategies and/or oral nutritional supplements. Our study observed 82.2% and 75.5% overall adequacies for energy and protein intake. In the studies mentioned before, intake was even lower: patients only met up to 66% and 60% of prescribed energy and protein targets (79,80). When no oral supplements were provided, energy and protein adequacies were notably worse: 37% and 48%, respectively (79).

Additionally, the ordered amount of food failed to meet the predicted targets. In patients failing to meet protein prescriptions (adequacy <90%), we found that the amount of protein ordered was significantly less than prescribed (median 1.17 versus 1.33 g/kg IBW*day; p=0.018). In addition, prescriptions were below recommended protein intake of at least 1.5g/kg*day (74,84). Similar findings were reported by Mitchell *et al.,* who demonstrated that neither prescriptions nor delivery of EN met targets in the post-ICU hospitalisation period (85).

Conversely, the best intake was seen in patients with (supplemental) enteral nutrition (EN); these patients all reached energy and protein adequacies >90%. This observation is concordant with findings reported by Chapple *et al.* and Ridley *et al.,* who demonstrated adequacies of 89-104% and 76-99% for energy and protein targets, respectively, in

patients receiving supplemental EN (78,79). Of note, not all EN patients reached their targets. Clinicians should consider that the average data shows that patients with the highest adequacies may conceal the insufficient nutritional intake of individual patients with the lowest intake.

Premature termination of EN

In **Chapter 6** we noted that EN was terminated in most cases (81.3%) due to (supposed) sufficient energy and protein intake. However, 38.5% of these patients had an overall median protein adequacy of <90% before discontinuation. After EN discontinuation, the most significant drop in intake was seen during the first day. Patients needed an additional six days to increase intake to meet protein targets again. After discontinuation of EN, the amounts of energy and proteins ordered by patients increased significantly. However, this was still insufficient to reach prescribed targets (median adequacy to energy and protein targets: 81.8% and 90.4%, respectively). We could not find any other studies focusing on the transition phase from EN to oral intake in the post-ICU convalescence, nor the reasons for removing the feeding tube.

Associations with clinical outcomes

Regarding clinical outcomes, no statistically significant difference was found in our study between patients reaching less or more than 90% of prescribed protein targets. This lack of significance might be due to an underpowered study population, as inclusions had to be stopped prematurely due to the COVID-19 pandemic. However, in current literature in and outside critical care, it has been demonstrated that individualized nutritional support results in enhanced energy and protein intake and lowers the risk of adverse outcomes and mortality (86,87). Furthermore, Wittholz *et al.* studied nutritional intake and related outcomes (such as body weight, handgrip strength and quadriceps muscle thickness) in 28 ICU survivors requiring mechanical ventilation for ≥48 hours after major trauma (81). They reported inadequate energy and protein adequacies (64% (SD 28%) and 72% (SD 32%) of targets, respectively) in the first five days post-ICU discharge. In addition, they noticed a significant weight reduction (mean 2.6 kg, 95% CI 1.0-4.2, $p = 0.004$) and loss of quadriceps muscle layer thickness (0.23 cm, 95% CI 0.06-0.4, $p = 0.01$) in this period. However, no association with protein intake was demonstrated. Findings should be interpreted cautiously due to the study's observational design (residual confounding). Likewise, Chapple and colleagues documented a correlation between greater quadriceps muscle layer thickness at hospital discharge and self-reported physical function three months after discharge (88).

Consequences for (post-)critical care nutrition

The observations of these studies examining intake in the post-ICU period have consequences for recommendations and guidelines on (post-)critical care nutrition and

future research. First, healthcare professionals should be(come) aware that this patient group often has a poor intake (89). Therefore, we suggest daily monitoring intake (from all nutritional routes), although this may be time-consuming and challenging. Secondly, we recommend gradually tapering EN intake and stopping EN only when oral intake has been proven sufficient, as Ridley *et al.* suggested (90). Subsequently, intake should be supported with food fortification or ONS, possibly prolonged after hospital discharge, to facilitate recovery (14,76,90). When targets are not reached after EN cessation, the reintroduction of EN should be considered in selected cases. This recommendation also implies that the feeding tube should be replaced when a gastric tube is removed accidentally (such as in delirium). Moreover, the importance of ordering and consuming adequate nutritional energy, including proteins, should be emphasised. Clinicians should consider that the prescribed calories and proteins are neither ordered nor consumed.

9.2.5 Progress of mitochondrial function during critical illness – implications for nutritional support

The acute phase of critical illness is hallmarked by enormous endogenous energy production. Simultaneously, demands are lower as the body's metabolism is downregulated, probably as a protective mechanism against severe stress ('bioenergetic downregulation'). A decreased mitochondrial respiration has been demonstrated in various cells in septic ICU patients, including muscle tissue and blood platelets (91–98). However, studies that measured mitochondrial function in peripheral blood mononuclear cells (PBMCs), which play an essential role in the initial (hyper)inflammatory response that hallmarks sepsis, have resulted in conflicting results (91,99–101).

The earliest signs of altered mitochondrial function may be observed within the first 24 hours of ICU admission (97). It is hypothesised that mitochondria cannot utilise substrates in this phase, and early aggressive feeding will result in "nutritrauma" as demonstrated by several recent randomised controlled trials (8–10). Therefore, mitochondrial dysfunction and disturbed homeostasis, observed in sepsis, have consequences for nutritional therapy.

However, limited studies investigated the progression of mitochondrial function during sepsis (including early and late acute phases) in correlation with clinical outcomes. In **Chapter 7**, we hypothesised that sepsis severity and survival are inversely associated with mitochondrial respiratory function in PBMCs. Surprisingly, the results of the MIC study argued against bio-energetic downregulation in these cells during sepsis. We demonstrated a higher basal and ATP-linked respiration during the first 48 hours of ICU admission in septic patients compared to their sex- and age-matched controls. In addition, a progressive increase in mitochondrial PBMC respiration during the first week

of ICU admission was associated with higher 3-month mortality rates. Therefore, the current results suggest that the upregulation of basal respiration may serve as a proxy marker for sepsis severity and outcomes.

Of note, our findings should be interpreted with caution. We used PBMCs as a model for all tissues. However, PBMCs are important cells during inflammation and systemic infection. They may have a different metabolic response to sepsis compared to other tissues directly involved in multiorgan failure, such as the liver and muscle (92). Therefore, these findings cannot be generalised to model mitochondrial function in sepsis in other tissues.

Similar to our observations, Sjövall *et al.* and Belikova *et al.* demonstrated that basal respiration was significantly increased within the first 48 hours of admission (99,100). In addition, Sjövall found a progressive increase in basal and maximal respiration. Strikingly, they observed no differences between survivors and non-survivors at any time point.

Methodological variety

In contrast to these findings, several other studies investigating the mitochondrial function of PBMCs in septic conditions observed a significant reduction in mitochondrial respiration (91,92,101). These conflicting findings may be due to methodological variety, including differences in the composition of the control group and respiration measurement methods. Although we could not identify consistent methodological differences among all the studies mentioned, combining these methodological differences can contribute to the contrasting results, as described in **Chapter 7**.

Our observations may contradict the speculation that mitochondrial dysfunction is the root cause of immunoparalysis and could be responsible for the onset of organ dysfunction (102). Still, pathophysiological interpretation of the difference in the increase of basal and ATP-linked respiration between survivors and non-survivors is precarious. The higher increase over time may partially be due to a lower basal and ATP-linked respiration in PBMCs at T1 of non-survivors compared to survivors, although this was not statistically significant. Disregarding possible differences at T1, a higher increase in both respiration parameters over time could reflect differences in the development of the infection or indicate immune dysfunction. However, the study results described in **Chapter 7** do not provide clarity in this respect, especially since immune mechanisms during sepsis are complex, consisting of simultaneous hyperinflammation and immune suppression. Future studies should take these hypotheses into account.

9.2.6 Mitochondrial function during critical illness – implications for sedation

The sepsis-induced bioenergetic downregulation, observed in several other tissue types, may be worsened by iatrogenic mitochondrial dysfunction, aggravating multiple organ failure and thus influencing clinical outcomes (93,94,97,103,104).

Animal models and studies conducted on human skeletal muscle cells have shown that the commonly used sedative drug propofol harms mitochondrial function. It achieves this by inhibiting the beta-oxidation of free fatty acids and impairing the function of respiratory chain complexes (105–110). Theoretically, this effect of propofol on mitochondria adversely impacts clinical outcomes, such as mortality and ICU-acquired weakness (ICU-AW), and thus, the need for a tracheostomy to wean from mechanical ventilation. Furthermore, patients with ICU-AW are more likely to be discharged to rehabilitation centres or nursing homes. However, in **Chapter 8** we describe that we found no statistically significant association between prolonged propofol administration and 6-month mortality. An association with secondary outcomes was neither demonstrated, such as duration of mechanical ventilation and need for a tracheostomy to wean from mechanical ventilation, ICU and hospital LOS, discharge destinations, and ICU, in-hospital, and 3-month mortality. These findings are similar to current literature, although available studies show inconsistent results in heterogeneous patient groups, making a thorough comparison with our study population difficult (111–113). In a recent meta-analysis of 252 RCTs, including 30,757 patients, all-cause mortality in postoperative and critically ill patients receiving propofol versus any other sedative agent was studied (114). They found that propofol significantly increases mortality in non-ICU patients, as they reported higher mortality rates in the propofol group versus the comparator groups (5.2% versus 4.3%; risk ratio = 1.10; 95% confidence interval 1.01-1.20; p=0.03), number needed to harm 235). However, no significant difference in mortality was observed in the ICU patient group (52/252 of studies, 21%; risk ratio not reported).

No studies have been published investigating associations between propofol administration and clinical outcomes, such as the need for a tracheostomy to wean from mechanical ventilation and discharge destinations.

Our observations in **Chapter 8** have consequences for sedation protocols in ICUs worldwide. Some clinicians warn of propofol-induced suppression of mitochondrial function, which may translate into adverse clinical outcomes such as ICU-AW and mortality. However, our data do not support this. We observed that prolonged sedation with propofol guided by RASS scores and sedation interruptions during the first week of

ICU admission of the least sick (as evaluated by clinical staff) critically ill adult patients mechanically ventilated for seven days or more seems safe.

Our results may indicate that the effect of propofol on mitochondrial function is limited and does not translate into a relevant impact on muscle function and ICU-acquired weakness and, as such, does not affect clinical outcomes. Another explanation could be that the effect on mitochondrial function is reversible: propofol's early pharmacological suppression of mitochondrial function may facilitate an adaptive process. When propofol administration is stopped, the mitochondrial function may recover.

9.3 Methodological considerations

Some methodological considerations should be considered when interpreting the results of the work described in this thesis.

9.3.1 Study design

First, a recurrent limitation mentioned in the chapters of this thesis is the lack of more extensive, multicentre, randomised controlled trials to confirm the hypotheses generated by our study results. All studies were single-centre, thereby limiting external validity. Moreover, studies were primarily retrospective, introducing several types of confounding and bias.

As such, in **Chapter 8**, significant baseline differences between the prolonged propofol and no prolonged propofol groups were observed, which introduced residual confounding and confounding by indication as indicated by the survival benefit in the propofol group in univariable analysis. Moreover, we could not correct the possible effects of any other medication administered (except for muscle relaxants or chronic steroids), which is also mentioned in **Chapter 7**. Similarly, in **Chapter 5**, we reported no association between protein intake and short-term outcomes, such as ICU or 3-month mortality, although an association with 6-month mortality was demonstrated. Again, the most plausible explanation is that additional confounding factors were not accounted for (residual confounding).

In addition, there was a significant risk of selection bias due to excluding patients with early mortality and early alive ICU discharge (predefined exclusion criteria: mechanical ventilation <7 days) in **Chapters 5** and **8**. Similarly, in **Chapter 6**, any patient who received exclusively oral nutrition during ICU stay was excluded since we were interested in patients who transitioned to this oral nutritional mode. Additionally, it was believed that patients receiving exclusive oral nutrition had lower disease severity,

and it was hypothesised that these patients could ramp up oral feeding more rapidly after ICU discharge than patients on (prolonged) medical nutrition. Thirdly, the long study period (2011-2018) in **Chapter 5**, including a defined change in nutrition delivery through adopting the electronic energy restriction protocol, may have contributed to the heterogeneous study population and other biases. Fourthly, we might have introduced bias by defining the cut-off values in **Chapters 5** and **8**; the outcome may depend on how well the cut-off values have been chosen (16). In **Chapter 6** we also mentioned participants' bias among patients with oral nutrition. Patients were aware that their intake was measured daily. We tried to eliminate recall bias as oral nutrition was objectively quantified through pre- and post-meal pictures. This study design might have introduced an observer's bias, although pictures were assessed by two researchers independently after completing the study participation. Finally, statistical bias was encountered in **Chapter 3** due to static measurements on three separate days in ICU patients with dynamic (metabolic) demands, resulting in changes in (clinical) conditions between measurements.

9.3.2 Study populations

All patients for the studies described in this thesis were recruited from the mixed medical-surgical ICU of Gelderse Vallei hospital (ZGV, Ede, The Netherlands). The inclusion of exclusively critically ill patients who were mechanically ventilated for at least two (**Chapter 3**) or at least seven days (**Chapters 5** and **8**) or who received (par) enteral feeding for ≥24 hours during ICU stay (**Chapter 6**) additionally limited external validity.

9.3.3 Assessment of energy requirements

Energy targets for the study populations in **Chapters 5, 6 and 8** were based on predictive equations instead of IC. As mentioned, predictive equations are population-based averages and are inaccurate compared to indirect calorimetry, not accounting for individual needs (3,20–22).

9.3.4 Assessment of nutritional intake

Accurate dietary intake assessment is essential but can be challenging and time-consuming. Several subjective and objective measures are available, each having limitations and biases (115). In **Chapter 6**, oral nutrition was objectively quantified using daily pre- and post-meal photographs, which helped to eliminate recall bias. The assessment of oral nutrition was carried out by two independent researchers who evaluated the pictures after the participants completed their involvement in the study, thus minimising observer bias. However, missing data (due to missing products or pictures) were extrapolated using less reliable methods, which contributed to bias.

9.4 Future research directions

9.4.1 In general

Several future research directions can be proposed from the work described in this thesis. Firstly, multicentre and high-quality randomised trials or prospective studies are needed to confirm our findings.

Secondly, our findings emphasise the importance of individual nutritional support, as there seems to be no "one size fits all". However, the ICU population is heterogeneous, and identifying patients most likely to benefit from certain nutritional interventions is challenging. Analyses of specific patient subgroups of interest may be valuable, and nutrition risk scores (such as the NUTRIC and NRS 2002 scores), body composition and pre-ICU nutrition status should be included. Moreover, the different phases of critical illness (acute versus (early) late)) should be taken into account. Determining the total prescribed calorie intake should be guided by individual estimations of resting energy expenditure, which are best measured through indirect calorimetry rather than relying on predictive equations. Also, non-intentional calories (glucose, propofol and citrate) should be evaluated and added to the energy dose (116).

Thirdly, parameters such as muscle mass, physical and functional performance, and other relevant parameters for (short- and long-term) quality of life should be used as primary outcomes in future clinical trials, not just the total amount of calories and proteins delivered. As such, Davies and coworkers have proposed an internationally agreed-upon minimum set of core outcomes to measure (amongst other things) physical function and QoL in nutritional and metabolic clinical research in critically ill patients (the CONCISE core outcome set) (117).

9.4.2 ICU nutrition

Adequate estimations of energy requirements

Further studies are needed to evaluate accuracy, bias, and precision at high levels of FiO_2 (≥85%) of easy-to-use novel bedside systems with IC functionality (such as the Beacon Care system) to make IC the standard of care in all hospitals without exception (**Chapter 2**). The novel ICs should be validated against the absolute gold standard. In addition, further research is warranted to make IC reliable for the most critically ill patients requiring organ support treatments, such as extracorporeal membrane oxygenation (ECMO) (24,118,119).

Moreover, future studies should focus on how we can estimate endogenous energy production in the acute phases of critical illness and adapt nutritional therapy for this.

Finally, it would be of great interest to measure body weight and body composition concomitantly to observe the effect of IC-guided energy intake (24). Bioelectric Impedance Assessment (BIA) is a promising bedside technique to perform this (120).

Optimisation of feeding tube placement

Regarding feeding tube placement using real-time video-assisted technology, the device should be made more suitable for post-pyloric (including nasojejunal) placement, for example, by adding a (magnetic) technique to move the tip of the feeding tube (mini-endoscope). Moreover, routine administration of prokinetics in patients with gastroparesis could make the technique more successful. Furthermore, image quality should be improved to distinguish the antrum-pylorus-duodenum better, aiming to make X-rays redundant to conform to the proper post-pyloric placement and check for the correct position when migration is suspected. Artificial intelligence techniques for processing and analysis of images may further enhance this. Finally, a study reporting accurate cost-effectiveness analyses of the IRIS technology feeding tubes is recommended, as well as a cost comparison study of the IRIS technology, Cortrak and gastro-endoscopy methods.

Protein intake in RH

This thesis describes a survival benefit for patients with RH who received a low protein diet (≤0.71 g/kg*day) during the first three days of ICU admission. Until now, explanatory mechanisms are lacking for this time- and dose-dependent effect of protein intake on clinical outcomes in critically ill patients. Future research should study the effect of calories and macronutrient intake (such as proteins) separately, focussing on underlying mechanisms to unravel this effect. Moreover, these studies could include biomarkers of optimal protein intake, such as nitrogen balance, physical function tests, body composition, and clinical outcomes. Imaging techniques like ultrasound, computed tomography, or BIA, could also guide protein dosing.

Metabolic consequences of RH

Previous studies from Olthof *et al.* and Doig *et al.* demonstrated an improved overall survival time for patients with RH receiving hypocaloric feeding (55,56). In our data, only a trend in favour of the caloric-restricted group was found. In these three studies, the Kaplan-Meier survival curves from patients on hypocaloric restriction versus full support did not separate during the early phase of the emergence of electrolyte abnormalities and the RH diagnosis. Conversely, mortality rates seem to separate two weeks after the diagnosis, suggesting that not the acute electrolyte abnormalities play a significant role, but the metabolic consequences of RH are more critical. The exact mechanism of these observations warrants further research.

9.4.3 Post-ICU nutrition

We recommend further studies to extend individualized multimodal nutritional support strategies to reach energy and protein targets post-ICU. These strategies should include, amongst others, measuring resting energy expenditure and body composition to determine the optimal energy and protein targets in every phase of disease and convalescence. Furthermore, strategies to improve intake are warranted. Current strategies, such as oral nutritional supplements, were mainly investigated in heterogeneous groups of hospital patients and demonstrated no benefit in mortality, complications or gain of weight (89,121). However, this evidence should be extended to ICU survivors.

In addition, future studies are required to examine the association between reached targets and clinical outcomes. We hypothesise that higher protein and energy intake is better in the post-acute phase as ATP production has improved, muscle protein synthesis is no longer depressed due to less anabolic resistance, and inflammation has resolved. A promising component of future nutritional therapy is the combination of nutrition and mobilisation, and exercise. Smiles *et al.* demonstrated in 29 sedentary, overweight, healthy male volunteers that lipid-induced anabolic resistance to protein administration reduced after exercise (122). However, this also has to be studied in the post-ICU recovery phase, including its effect on clinical outcomes (123,124). Finally, more insight is needed into patient factors contributing to nutritional intake, such as a change in taste, appetite, and satiety (79,125–127).

Recently, the digital photography method has been proven valid and accurate for non-trained observers (ValiFood study, personal communication), similar to results reported by Winzer *et al.* (128) It was compared to the current gold standard (weighed food record charts), with a variation of 20% considered acceptable. However, there was significant variation in the evaluation of separate items, particularly the semi-solids, which should be improved. Moreover, this method is labour-intensive and has disadvantages and limitations, such as technical camera problems, missing pictures, and difficulties assessing opaque packaging. Alternative methods which are easier to implement, such as digital food record charts filled in at the bedside by the nurses, should be considered. This method was also demonstrated to be accurate in the ValiFood study. In addition, digital food recognition and weight estimation using portable devices are promising techniques and warrant further development, including automatic calculations of energy and proteins consumed and immediate feedback loops to clinicians, dieticians, and patients (129).

9.4.4 (Progression of) mitochondrial function

New studies are warranted to unravel the interplay between mitochondrial respiration, biogenesis and sepsis in several tissue and cell types. These future studies should focus on (the progression of) mitochondrial function, dynamics, and autophagy, including genomic and proteomic profiling of mitochondrial dynamics and autophagy factors. Moreover, additional basic research is needed to elucidate the effect of propofol on mitochondrial function. In addition, future randomised controlled trials are necessary to confirm our findings (minimising residual confounding) that propofol and other medications, which may suppress mitochondrial function, are safe for prolonged administration in critically ill patients, including possible associations with outcomes such as ICU-AW and discharge destinations.

9.5 Last but not least

Long-term patient survival is the ultimate goal of critical care medicine. However, due to the observation that despite the lower mortality among ICU patients over the last decades, the number of patients who cannot return home but have to be transferred to nursing homes or rehabilitation centres has tripled, the focus should shift more to functional recovery and quality of life (QoL). Nutrition therapy can make a difference in all critical illness and convalescence phases. Personalised, targeted nutritional therapy will reduce the adverse effects of feeding and provide the essential substrate for recovery. Nutritional therapy should be provided at the right time to the right patient, using the correct dose and with the optimal nutrients.

To contribute to this, this thesis aimed to increase knowledge about the nutritional journey of ICU and post-ICU patients. Several steps in nutritional therapy during and after ICU stay were investigated, including some metabolic interactions of macronutrient administration and the evolution of mitochondrial dysfunction during sepsis as this has consequences for nutritional support.

From the results of this thesis, three final recommendations are made. Firstly, nutritional support should be individualized using the correct doses adapted to the patients' dynamic needs during the several phases of critical illness and convalescence. Therefore, dosing of calories and macronutrients should begin a proper understanding of mitochondrial function. Moreover, repeated adequate measurements of caloric needs are necessary; novel techniques may be helpful for this. Secondly, nutritional support should be individualized using the optimal nutrients. As such, when refeeding hypophosphatemia is encountered in critical illness, not only caloric restriction is warranted for some days,

but also protein intake should be restricted. Finally, individualized nutritional support to reach energy and protein targets should be extended in the post-ICU period.

In this way, patient- and phase-targeted nutritional strategies in both ICU and convalescence will contribute to the ultimate goal to improve long-term outcomes and QoL of ICU survivors.

References

1. Weijs PJM, Looijaard WGPM, Beishuizen A, Girbes ARJ, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014 Dec 14;18(6):701.
2. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016 Nov 10;20(1):367.
3. Segadilha NLAL, Rocha EEM, Tanaka LMS, Gomes KLP, Espinoza REA, Peres WAF. Energy Expenditure in Critically Ill Elderly Patients: Indirect Calorimetry vs Predictive Equations. Journal of Parenteral and Enteral Nutrition. 2016;41(5):776–84.
4. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clinical Nutrition. 2019;38(1):48–79.
5. Duan JY, Zheng WH, Zhou H, Xu Y, Huang HB. Energy delivery guided by indirect calorimetry in critically ill patients: a systematic review and meta-analysis. Crit Care. 2021 Feb 27;25(1):88.
6. Pertzov B, Bar-Yoseph H, Menndel Y, Bendavid I, Kagan I, Glass YD, et al. The effect of indirect calorimetry guided isocaloric nutrition on mortality in critically ill patients—a systematic review and meta-analysis. Eur J Clin Nutr. 2021;76(1):5–15.
7. De Waele E, van Zanten ARH. Routine use of indirect calorimetry in critically ill patients: pros and cons. Crit Care. 2022 May 5;26(1):123.
8. Yébenes JC, Campins L, Martínez de Lagran I, Bordeje L, Lorencio C, Grau T, et al. Nutritrauma: A Key Concept for Minimising the Harmful Effects of the Administration of Medical Nutrition Therapy. Nutrients. 2019 Aug 1;11(8):1775.
9. Moonen HPFX, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: consequences for nutrition therapy. Curr Opin Crit Care. 2020;26(4):346–54.
10. McClave SA, Wischmeyer PE, Miller KR, van Zanten ARH. Mitochondrial Dysfunction in Critical Illness: Implications for Nutritional Therapy. Curr Nutr Rep. 2019;8(4):363–73.
11. Van Dyck L, Casaer MP, Gunst J. Autophagy and Its Implications Against Early Full Nutrition Support in Critical Illness. Nutrition in Clinical Practice. 2018;33(3):339–47.
12. McKeever L, Bonini M, Braunschweig C. Feeding During Phases of Altered Mitochondrial Activity: A Theory. Journal of Parenteral and Enteral Nutrition. 2017;42(5):855–63.
13. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute Skeletal Muscle Wasting in Critical Illness. JAMA. 2013;310(15):1591.
14. Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. Crit Care. 2017 Dec 28;21(Suppl 3):316.
15. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma. Crit Care Med. 1999;27(7):1295–302.
16. Weijs PJM, Wischmeyer PE. Optimizing energy and protein balance in the ICU. Curr Opin Clin Nutr Metab Care. 2013;16(2):194–201.
17. Niederer LE, Miller H, Haines KL, Molinger J, Whittle J, MacLeod DB, et al. Prolonged progressive hypermetabolism during COVID-19 hospitalization undetected by common predictive energy equations. Clin Nutr ESPEN. 2021/08/03. 2021 Oct;45:341–50.
18. De Waele E, Jonckheer J, Wischmeyer PE. Indirect calorimetry in critical illness: a new standard of care? Curr Opin Crit Care. 2021 Aug 1;27(4):334–43.

19. Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. J Intensive Care. 2021 Jan 12;9(1):8.
20. Flack KD, Siders WA, Johnson L, Roemmich JN. Cross-Validation of Resting Metabolic Rate Prediction Equations. J Acad Nutr Diet. 2016;116(9):1413–22.
21. Wichansawakun S, Meddings L, Alberda C, Robbins S, Gramlich L. Energy requirements and the use of predictive equations versus indirect calorimetry in critically ill patients. Applied Physiology, Nutrition, and Metabolism. 2015;40(2):207–10.
22. Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: A retrospective validation. Clinical Nutrition. 2019;38(3):1206–10.
23. De Waele E, Spapen H, Honoré PM, Mattens S, Van Gorp V, Diltoer M, et al. Introducing a new generation indirect calorimeter for estimating energy requirements in adult intensive care unit patients: Feasibility, practical considerations, and comparison with a mathematical equation. J Crit Care. 2013;28(5):884.e1-884.e6.
24. Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clinical Nutrition. 2017;36(3):651–62.
25. Poulsen MK, Thomsen LP, Kjærgaard S, Rees SE, Karbing DS. Reliability of, and Agreement Between, two Breath-by-Breath Indirect Calorimeters at Varying Levels of Inspiratory Oxygen. Nutrition in Clinical Practice. 2019;34(5):767–74.
26. Berger MM, Reintam-Blaser A, Calder PC, Casaer M, Hiesmayr MJ, Mayer K, et al. Monitoring nutrition in the ICU. Clinical Nutrition. 2019;38(2):584–93.
27. Jonckheer J, Spapen H, Malbrain MLNG, Oschima T, De Waele E. Energy expenditure and caloric targets during continuous renal replacement therapy under regional citrate anticoagulation. A viewpoint. Clinical Nutrition. 2020;39(2):353–7.
28. Jonckheer J, Demol J, Lanckmans K, Malbrain MLNG, Spapen H, De Waele E. MECCIAS trial: Metabolic consequences of continuous veno-venous hemofiltration on indirect calorimetry. Clinical Nutrition. 2020;39(12):3797–803.
29. Rousseau AF, Fadeur M, Colson C, Misset B. Measured Energy Expenditure Using Indirect Calorimetry in Post-Intensive care unit Hospitalized Survivors: A Comparison with Predictive Equations. Nutrients. 2022 Sep 25;14(19):3981.
30. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. Journal of Parenteral and Enteral Nutrition. 2003;27(5):355–73.
31. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. Journal of Parenteral and Enteral Nutrition. 2016;40(2):159–211.
32. Silk DBA. The Evolving Role of Post–Ligament of Trietz Nasojejunal Feeding in Enteral Nutrition and the Need for Improved Feeding Tube Design and Placement Methods. Journal of Parenteral and Enteral Nutrition. 2011;35(3):303–7.
33. Roberts S, Echeverria P, Gabriel SA. Devices and Techniques for Bedside Enteral Feeding Tube Placement. Nutrition in Clinical Practice. 2007;22(4):412–20.
34. Halloran O, Grecu B, Sinha A. Methods and Complications of Nasoenteral Intubation. Journal of Parenteral and Enteral Nutrition. 2010;35(1):61–6.

35. Powers J, Fischer MH, Ziemba-Davis M, Brown J, Phillips DM. Elimination of Radiographic Confirmation for Small-Bowel Feeding Tubes in Critical Care. American Journal of Critical Care. 2013;22(6):521–7.
36. Lamont T, Beaumont C, Fayaz A, Healey F, Huehns T, Law R, et al. Checking placement of nasogastric feeding tubes in adults (interpretation of x ray images): summary of a safety report from the National Patient Safety Agency. BMJ. 2011;342(may05 1):d2586–d2586.
37. Powers J, Luebbehusen M, Spitzer T, Coddington A, Beeson T, Brown J, et al. Verification of an Electromagnetic Placement Device Compared With Abdominal Radiograph to Predict Accuracy of Feeding Tube Placement. Journal of Parenteral and Enteral Nutrition. 2011;35(4):535–9.
38. National Patient Safety Agency. Reducing the harm caused by misplaced nasogastric feeding tubes in adults, children and infants [Internet]. [cited 2024 Jun 6]. Available from: http://www.gbukenteral.com/pdf/NPSA-Alert-2011.pdf
39. Sparks DA, Chase DM, Coughlin LM, Perry E. Pulmonary Complications of 9931 Narrow-Bore Nasoenteric Tubes During Blind Placement. Journal of Parenteral and Enteral Nutrition. 2011;35(5):625–9.
40. Gerritsen A, van der Poel MJ, de Rooij T, Molenaar IQ, Bergman JJ, Busch OR, et al. Systematic review on bedside electromagnetic-guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes. Gastrointest Endosc. 2015;81(4):836-847.e2.
41. Holzinger U, Brunner R, Miehsler W, Herkner H, Kitzberger R, Fuhrmann V, et al. Jejunal tube placement in critically ill patients: A prospective, randomized trial comparing the endoscopic technique with the electromagnetically visualized method. Crit Care Med. 2011;39(1):73–7.
42. Wischmeyer PE, McMoon MM, Waldron NH, Dye EJ. Successful Identification of Anatomical Markers and Placement of Feeding Tubes in Critically Ill Patients via Camera-Assisted Technology with Real-Time Video Guidance. JPEN J Parenter Enteral Nutr. 2018/06/20. 2019 Jan;43(1):118–25.
43. Taylor SJ, Sayer K, Terlevich A, Campbell D. Tube placement using 'IRIS': A pilot assessment of its utility and safety. Intensive Crit Care Nurs. 2021;66:103077.
44. Mizzi A, Cozzi S, Beretta L, Greco M, Braga M. Real-time image-guided nasogastric feeding tube placement: A case series using Kangaroo with IRIS Technology in an ICU. Nutrition. 2017;37:48–52.
45. Cardona E, Mehta S. Bedside postpyloric enteral tube placement using Kangaroo IRIS technology: a single-center case series. Nutrition. 2021/02/11. 2021 Jun;86:111195.
46. Taylor SJ, Milne D, Zeino Z, Griffiths L, Clemente R, Greer-Rogers F, et al. An externally validated guide to anatomical interpretation using a direct-vision ('IRIS') feeding tube. Clin Nutr ESPEN. 2024;60:356–61.
47. Taylor S, Sayer K, Milne D, Brown J, Zeino Z. Integrated real-time imaging system, "IRIS", Kangaroo feeding tube: a guide to placement and image interpretation. BMJ Open Gastroenterol. 2021 Oct;8(1):e000768.
48. Karpasiti T, Shepherd SJ. Bedside post-pyloric tube placement using direct visualisation in mechanically ventilated patients: A single centre case series. Intensive Crit Care Nurs. 2022;70:103222.
49. Wei Y, Jin Z, Zhu Y, Hu W. Electromagnetic-guided versus endoscopic placement of post-pyloric feeding tubes: a systematic review and meta-analysis of randomised controlled trials. J Intensive Care. 2020 Dec 10;8(1):92.

50. Kappelle WFW, Walter D, Stadhouders PH, Jebbink HJA, Vleggaar FP, van der Schaar PJ, et al. Electromagnetic-guided placement of nasoduodenal feeding tubes versus endoscopic placement: a randomized, multicenter trial. Gastrointest Endosc. 2018;87(1):110–8.
51. National Institute for Health and Care Excellence. CORTRAK 2 Enteral Access System for placing nasoenteral feeding tubes [Internet]. 2016 [cited 2024 Jun 6]. Available from: nice.org.uk/guidance/mib48
52. Kaffarnik MF, Lock JF, Wassilew G, Neuhaus P. The use of bedside electromagnetically guided nasointestinal tube for jejunal feeding of critical ill surgical patients. Technology and Health Care. 2013;21(1):1–8.
53. Gerritsen A, de Rooij T, Dijkgraaf MG, Busch OR, Bergman JJ, Ubbink DT, et al. Electromagnetic-Guided Bedside Placement of Nasoenteral Feeding Tubes by Nurses Is Non-Inferior to Endoscopic Placement by Gastroenterologists: A Multicenter Randomized Controlled Trial. American Journal of Gastroenterology. 2016;111(8):1123–32.
54. Hemington-Gorse SJ, Sheppard NN, Martin R, Shelley O, Philp B, Dziewulski P. The use of the Cortrak Enteral Access System™ for post-pyloric (PP) feeding tube placement in a Burns Intensive care unit. Burns. 2011;37(2):277–80.
55. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clinical Nutrition. 2018;37(5):1609–17.
56. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3(12):943–52.
57. Koekkoek WAC (Kristine), van Setten CH (Coralien), Olthof LE, Kars JCN (Hans), van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study. Clinical Nutrition. 2019;38(2):883–90.
58. Lee ZY, Dresen E, Lew CCH, Bels J, Hill A, Hasan MS, et al. The effects of higher versus lower protein delivery in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. Crit Care. 2024 Jan 6;28(1):15.
59. Bendavid I, Zusman O, Kagan I, Theilla M, Cohen J, Singer P. Early Administration of Protein in Critically Ill Patients: A Retrospective Cohort Study. Nutrients. 2019 Jan 7;11(1):106.
60. Weijs PJM, Looijaard WGPM, Beishuizen A, Girbes ARJ, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014 Dec 14;18(6):701.
61. Arabi YM, Al-Dorzi HM, Sadat M. Protein intake and outcome in critically ill patients. Current Opinion in Clinical Nutrition & Metabolic Care. 2020;23(1):51–8.
62. Preiser JC, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015 Jan 29;19(1):35.
63. Tsai JR, Chang WT, Sheu CC, Wu YJ, Sheu YH, Liu PL, et al. Inadequate energy delivery during early critical illness correlates with increased risk of mortality in patients who survive at least seven days: A retrospective study. Clinical Nutrition. 2011;30(2):209–14.
64. Hoffer LJ. High-Protein Hypocaloric Nutrition for Non-Obese Critically Ill Patients. Nutrition in Clinical Practice. 2018;33(3):325–32.

65. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of Disease and Macronutrient Dose in the Randomized Controlled EPaNIC Trial. Am J Respir Crit Care Med. 2013;187(3):247–55.
66. Derde S, Vanhorebeek I, Güiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early Parenteral Nutrition Evokes a Phenotype of Autophagy Deficiency in Liver and Skeletal Muscle of Critically Ill Rabbits. Endocrinology. 2012;153(5):2267–76.
67. Thiessen SE, Derde S, Derese I, Dufour T, Vega CA, Langouche L, et al. Role of Glucagon in Catabolism and Muscle Wasting of Critical Illness and Modulation by Nutrition. Am J Respir Crit Care Med. 2017;196(9):1131–43.
68. Morton RW, Traylor DA, Weijs PJM, Phillips SM. Defining anabolic resistance: implications for delivery of clinical care nutrition. Curr Opin Crit Care. 2018;24(2):124–30.
69. Chapple L anne S, Kouw IWK, Summers MJ, Weinel LM, Gluck S, Raith E, et al. Muscle Protein Synthesis after Protein Administration in Critical Illness. Am J Respir Crit Care Med. 2022;206(6):740–9.
70. Haines RW, Fowler AJ, Wan YI, Flower L, Heyland DK, Day A, et al. Catabolism in Critical Illness: A Reanalysis of the REducing Deaths due to OXidative Stress (REDOXS) Trial*. Crit Care Med. 2022;50(7):1072–82.
71. Haines RW, Zolfaghari P, Wan Y, Pearse RM, Puthucheary Z, Prowle JR. Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma. Intensive Care Med. 2019;45(12):1718–31.
72. Page A, Flower L, Prowle J, Puthucheary Z. Novel methods to identify and measure catabolism. Curr Opin Crit Care. 2021;27(4):361–6.
73. Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW, et al. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017 Aug 26;21(1):226.
74. National Institute for Health and Excellence. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition [Internet]. 2006 [cited 2024 Jun 6]. Available from: https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#screening-for-malnutrition-and-the-risk-of-malnutrition-in-hospital-and-the-community
75. Bear DE, Wandrag L, Merriweather JL, Connolly B, Hart N, Grocott MPW, et al. The role of nutritional support in the physical and functional recovery of critically ill patients: a narrative review. Crit Care. 2017 Aug 26;21(1):226.
76. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care. 2019 Nov 21;23(1):368.
77. Obeid J, Ridley Emma, Hodgson C. Nutrition in the Post ICU Period: Where is the Evidence? ICU Manag Pract. 2020;20(4):283–7.
78. Chapple L anne S, Deane AM, Heyland DK, Lange K, Kranz AJ, Williams LT, et al. Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury. Clinical Nutrition. 2016;35(6):1315–22.
79. Ridley EJ, Parke RL, Davies AR, Bailey M, Hodgson C, Deane AM, et al. What Happens to Nutrition Intake in the Post–Intensive care unit Hospitalization Period? An Observational Cohort Study in Critically Ill Adults. Journal of Parenteral and Enteral Nutrition. 2018;43(1):88–95.
80. Moisey LL, Pikul J, Keller H, Yeung CYE, Rahman A, Heyland DK, et al. Adequacy of Protein and Energy Intake in Critically Ill Adults Following Liberation From Mechanical Ventilation Is Dependent on Route of Nutrition Delivery. Nutrition in Clinical Practice. 2020;36(1):201–12.

81. Wittholz K, Fetterplace K, Clode M, George ES, MacIsaac CM, Judson R, et al. Measuring nutrition-related outcomes in a cohort of multi-trauma patients following intensive care unit discharge. Journal of Human Nutrition and Dietetics. 2019;33(3):414–22.
82. De Waele E, Rosseel Z, Pen JJ. Post-ICU nutrition: the neglected side of metabolic support. Curr Opin Crit Care. 2023;29(4):360–2.
83. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of Oral Intake in Critically Ill Patients 1 Week after Extubation. J Am Diet Assoc. 2010;110(3):427–33.
84. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clinical Nutrition. 2019;38(1):10–47.
85. Mitchell A, Clemente R, Downer C, Greer F, Allan K, Collinson A, et al. Protein Provision in Critically Ill Adults Requiring Enteral Nutrition: Are Guidelines Being Met? Nutrition in Clinical Practice. 2018;34(1):123–30.
86. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualized nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. The Lancet. 2019;393(10188):2312–21.
87. Weijs PJM, Mogensen KM, Rawn JD, Christopher KB. Protein Intake, Nutritional Status and Outcomes in ICU Survivors: A Single Center Cohort Study. J Clin Med. 2019 Jan 4;8(1):43.
88. Chapple LAS, Deane AM, Williams LT, Strickland R, Schultz C, Lange K, et al. Longitudinal changes in anthropometrics and impact on self-reported physical function after traumatic brain injury. Critical Care and Resuscitation. 2017;19(1):29–36.
89. Nienow MK, Susterich CE, Peterson SJ. Prioritizing nutrition during recovery from critical illness. Current Opinion in Clinical Nutrition & Metabolic Care. 2020;24(2):199–205.
90. Ridley EJ, Chapple L anne S, Chapman MJ. Nutrition intake in the post-ICU hospitalization period. Current Opinion in Clinical Nutrition & Metabolic Care. 2020;23(2):111–5.
91. Japiassú AM, Santiago APSA, d'Avila J da CP, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, et al. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity*. Crit Care Med. 2011;39(5):1056–63.
92. Garrabou G, Morén C, López S, Tobías E, Cardellach F, Miró Ò, et al. The Effects of Sepsis on Mitochondria. J Infect Dis. 2011;205(3):392–400.
93. Supinski GS, Schroder EA, Callahan LA. Mitochondria and Critical Illness. Chest. 2019/09/05. 2020 Feb;157(2):310–22.
94. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence. 2013/11/01. 2014 Jan 1;5(1):66–72.
95. Singer M. Critical illness and flat batteries. Crit Care. 2017 Dec 28;21(Suppl 3):309.
96. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2017;1863(10):2534–45.
97. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. The Lancet. 2002;360(9328):219–23.
98. Exline MC, Crouser ED. Mitochondrial mechanisms of sepsis-induced organ failure. Front Biosci. 2008 May 1;13:5030–41.
99. Sjövall F, Morota S, Persson J, Hansson MJ, Elmér E. Patients with sepsis exhibit increased mitochondrial respiratory capacity in peripheral blood immune cells. Crit Care. 2013 Jul 24;17(4):R152–R152.

100. Belikova I, Lukaszewicz AC, Faivre V, Damoisel C, Singer M, Payen D. Oxygen consumption of human peripheral blood mononuclear cells in severe human sepsis *. Crit Care Med. 2007;35(12):2702–8.
101. Jang DH, Orloski CJ, Owiredu S, Shofer FS, Greenwood JC, Eckmann DM. Alterations in Mitochondrial Function in Blood Cells Obtained From Patients With Sepsis Presenting to an Emergency Department. Shock. 2019 May;51(5):580–4.
102. Nedel W, Deutschendorf C, Portela LVC. Sepsis-induced mitochondrial dysfunction: A narrative review. World J Crit Care Med. 2023 Jun 9;12(3):139–52.
103. Abdelmalik PA, Rakocevic G. Propofol as a Risk Factor for ICU-Acquired Weakness in Septic Patients with Acute Respiratory Failure. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2017;44(3):295–303.
104. Lönnqvist PA, Bell M, Karlsson T, Wiklund L, Höglund AS, Larsson L. Does prolonged propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? Br J Anaesth. 2020/06/10. 2020 Sep;125(3):e334–6.
105. Branca D, Roberti MS, Lorenzin P, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol on the oxidative phosphorylation of isolated rat liver mitochondria. Biochem Pharmacol. 1991;42(1):87–90.
106. Branca D, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol (propofol) on isolated rat heart mitochondria. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 1995;110(1):41–5.
107. Branca D, Roberti MS, Vincenti E, Scutari G. Uncoupling effect of the general anesthetic 2,6-diisopropylphenol in isolated rat liver mitochondria. Arch Biochem Biophys. 1991;290(2):517–21.
108. Rigoulet M, Devin A, Avéret N, Vandais B, Guérin B. Mechanisms of Inhibition and Uncoupling of Respiration in Isolated Rat Liver Mitochondria by the General Anesthetic 2,6-Diisopropylphenol. Eur J Biochem. 1996;241(1):280–5.
109. Krajčová A, Løvsletten NG, Waldauf P, Frič V, Elkalaf M, Urban T, et al. Effects of Propofol on Cellular Bioenergetics in Human Skeletal Muscle Cells. Crit Care Med. 2018;46(3):e206–12.
110. Fedorov A, Lehto A, Klein J. Inhibition of mitochondrial respiration by general anesthetic drugs. Naunyn Schmiedebergs Arch Pharmacol. 2022/11/17. 2023 Feb 17;396(2):375–81.
111. Ho KM, Ng JY. The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. Intensive Care Med. 2008;34(11):1969–79.
112. Kelly DF, Goodale DB, Williams J, Herr DL, Chappell ET, Rosner MJ, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. J Neurosurg. 1999;90(6):1042–52.
113. Garcia R, Salluh JIF, Andrade TR, Farah D, da Silva PSL, Bastos DF, et al. A systematic review and meta-analysis of propofol versus midazolam sedation in adult intensive care (ICU) patients. J Crit Care. 2021;64:91–9.
114. Kotani Y, Pruna A, Turi S, Borghi G, Lee TC, Zangrillo A, et al. Propofol and survival: an updated meta-analysis of randomized clinical trials. Crit Care. 2023 Apr 12;27(1):139.
115. McClung HL, Ptomey LT, Shook RP, Aggarwal A, Gorczyca AM, Sazonov ES, et al. Dietary Intake and Physical Activity Assessment: Current Tools, Techniques, and Technologies for Use in Adult Populations. Am J Prev Med. 2018;55(4):e93–104.
116. Bousie E, van Blokland D, Lammers HJW, van Zanten ARH. Relevance of non-nutritional calories in mechanically ventilated critically ill patients. Eur J Clin Nutr. 2016/09/14. 2016 Dec;70(12):1443–50.

117. Davies TW, van Gassel RJJ, van de Poll M, Gunst J, Casaer MP, Christopher KB, et al. Core outcome measures for clinical effectiveness trials of nutritional and metabolic interventions in critical illness: an international modified Delphi consensus study evaluation (CONCISE). Crit Care. 2022 Aug 6;26(1):240.
118. De Waele E, van Zwam K, Mattens S, Staessens K, Diltoer M, Honoré PM, et al. Measuring resting energy expenditure during extracorporeal membrane oxygenation: preliminary clinical experience with a proposed theoretical model. Acta Anaesthesiol Scand. 2015;59(10):1296–302.
119. De Waele E, Jonckheer J, Pen JJ, Demol J, Staessens K, Puis L, et al. Energy expenditure of patients on ECMO: A prospective pilot study. Acta Anaesthesiol Scand. 2018;63(3):360–4.
120. Moonen HPFX, Van Zanten ARH. Bioelectric impedance analysis for body composition measurement and other potential clinical applications in critical illness. Curr Opin Crit Care. 2021 Aug 1;27(4):344–53.
121. Feinberg J, Nielsen EE, Korang SK, Halberg Engell K, Nielsen MS, Zhang K, et al. Nutrition support in hospitalised adults at nutritional risk. Cochrane Database Syst Rev. 2017 May 19;5(5):CD011598–CD011598.
122. Smiles WJ, Churchward-Venne TA, Loon LJC, Hawley JA, Camera DM. A single bout of strenuous exercise overcomes lipid-induced anabolic resistance to protein ingestion in overweight, middle-aged men. The FASEB Journal. 2019;33(6):7009–17.
123. Fadeur M, Preiser JC, Verbrugge AM, Misset B, Rousseau AF. Oral Nutrition during and after Critical Illness: SPICES for Quality of Care! Nutrients. 2020 Nov 14;12(11):3509.
124. Flower L, Puthucheary Z. Muscle wasting in the critically ill patient: how to minimise subsequent disability. Br J Hosp Med. 2020;81(4):1–9.
125. Chapple L anne S, Weinel LM, Abdelhamid YA, Summers MJ, Nguyen T, Kar P, et al. Observed appetite and nutrient intake three months after ICU discharge. Clinical Nutrition. 2019;38(3):1215–20.
126. Merriweather JL, Salisbury LG, Walsh TS, Smith P. Nutritional care after critical illness: a qualitative study of patients' experiences. Journal of Human Nutrition and Dietetics. 2014;29(2):127–36.
127. Jarden RJ, Sutton-Smith L, Boulton C. Oral intake evaluation in patients following critical illness: an ICU cohort study. Nurs Crit Care. 2018;23(4):179–85.
128. Winzer E, Luger M, Schindler K. Using digital photography in a clinical setting: a valid, accurate, and applicable method to assess food intake. Eur J Clin Nutr. 2018;72(6):879–87.
129. Zhang Q, He C, Qin W, Liu D, Yin J, Long Z, et al. Eliminate the hardware: Mobile terminals-oriented food recognition and weight estimation system. Front Nutr. 2022 Nov 16;9:965801.

Appendices

List of abbreviations

95% CI	95% confidence interval
Acetyl-CoA	acetyl coenzyme A
ADP	adenosine diphosphate
APACHE II	Acute Physiology And Chronic Health Evaluation II
ARDS	acute respiratory distress syndrome
ATP	adenine triphosphate
AYR	At Your Request®
BIA	bioelectric impedance assessment
BMI	body mass index
CCCP	arbonyl cyanide m-chlorophenylhydrazone
CCI	Charlson Comorbidity Index
CIM	critical illness myopathy
CIP	critical illness polyneuropathy
COPD	chronic obstructive pulmonary disease
CPAX	Chelsea Critical Care Physical Assessment tool
DAMP	danger-associated molecular pattern
DNA	deoxyribonucleic acid
ECMO	extracorporeal membrane oxygenation
EE	energy expenditure
$EEVCO_2$	EE estimated by ventilator-derived carbon dioxide consumption
EN	enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
ETC	electron transport chain
FAD	flavin adenine dinucleotide
FAO/WHO	Food and Agricultural Organization / World Health Organization
FEV1	first second forced expiration
FFA	free fatty acid
FiO_2	fraction of inspired oxygen
FQ	food quotient
Fr	French
FVC	forced vital capacity
G	grams
GCS	Glasgow Coma Scale
HR	hazard ratio
IBW	ideal body weight
IC	indirect calorimetry
ICC	intraclass correlation coefficient
ICU	intensive care unit
ICU-AW	intensive care unit-acquired weakness
IQR	interquartile range
IRIS	Integrated Real-Time Imaging System
ITT	intention-to-treat
Kcal	kilocalories
Kg	kilograms
LMR	lymphocyte-monocyte ratio
LoA	limits of agreement
LOS	length of stay
mGHAA-9	modified Group Health Association of America-9
mNUTRIC	Modified Nutrition Risk In Critically ill
MRC	Medical Research Council
N	number
NAD	nicotinamide-adenine dinucleotide
NG	nasogastric
NICE	National Institute for Health and Care Excellence
NJ	nasojejunal
NUTRIC	Nutrition Risk in Critically ill
ONS	oral nutrition supplements
OR	odds ratio
OXPHOS	oxidative phosphorylation system
PBMC	peripheral blood mononuclear cell
PBQ	Patient-Beacon-Quark (measurement configuration)

PDMS	patient data management system
PEEP	positive end-expiratory pressure
PEQ	Patient Experience Questionnaire
PICS	post-intensive care syndrome
PN	parenteral nutrition
PP	per protocol
PQB	Patient-Quark-Beacon (measurement configuration)
PRIS	propofol infusion syndrome
QoL	quality of life
QS-PEQ	Generic Short Patient Experiences Questionnaire
RASS	Richmond Agitation Sedation Scale
RCT	randomized controlled trial
REE	resting energy expenditure
RER	respiratory exchange ratio
RFS	refeeding syndrome
RH	refeeding hypophosphatemia
ROS	reactive oxygen species
RQ	respiratory quotient
SAPS II	Simplified Acute Physiology Score
SARS-CoV-2	severe acute respiratory coronavirus 2
SD	standard deviation
SE	standard error
SOFA	Sequential Organ Failure Assessment
SUM	Single Usability Metric
TCA	tricarboxylic acid
TEE	total energy expenditure
UCR	urea-to-creatinine ratio
VCO_2	volume of carbon dioxide expired
VIF	variance inflation factor
VO_2	volume of oxygen inspired
WUR	Wageningen University and Research
ZGV	Ziekenhuis Gelderse Vallei (Gelderse Vallei hospital)

Summary

In the past, nutritional support in critically ill patients was regarded as exogenous fuel to preserve lean body mass and replace oral intake in those unable to eat. However, more recently, this strategy has evolved to nutritional therapy, in which nutrition helps to attenuate catabolism (and thus reduce muscle wasting) and maintain nutritional status to improve clinical outcomes. There is increasing evidence for time- and dose-dependent (and thus patient-targeted) nutrition – there is no "one size fits all". Critically ill patients preferably receive nutritional support matching their metabolic needs in the ICU and post-ICU period. However, this is complex as patients' caloric and macronutrient (such as protein) requirements vary significantly throughout their ICU journey and formal guidelines for the dynamic nutritional targets of (particularly post-)ICU patients still need to be developed. Therefore, this thesis aimed to increase knowledge about the nutritional journey of patients during the several (metabolic) phases of critical illness and throughout their hospitalisation period (from ICU admission until hospital discharge), with the ultimate goal of to improve current nutritional strategies and prevent adverse effects. A summary of the main findings described in this thesis is provided below.

Part I: Nutrition in the ICU

In the first part of this thesis, we investigated some strategies to optimise ICU nutrition, particularly determining energy requirements, safely inserting feeding tubes, and individualising nutritional support in patients with refeeding hypophosphatemia (RH).

Right dose

Critically ill patients' caloric and macronutrient (such as protein) requirements vary significantly throughout their ICU journey (1–4). Therefore, an individualized stepwise approach to provide calories and proteins during the several phases of critical illness is recommended, guided by accurate estimations of energy requirements(5). However, IC is unavailable in many hospitals due to costs or user difficulties, such as time-consuming calibration procedures (6,7). Novel bedside systems with modern and intuitive interfaces may overcome this problem. In **Chapter 2**, we compared an easy-to-use system (the Beacon Care system, Mermaid Care Company, Denmark) with the current device in our ICU (Deltatrac Metabolic Monitor, Datex, Helsinki, Finland). We found that the Beacon Care system IC accurately determined resting energy expenditure (REE) in mechanically ventilated critically ill patients compared to the Quark IC. Additionally, measured REE by IC was compared to calculated REE by predictive equations. The predictive equations performed poorly compared to both devices, underestimating the metabolic needs of mechanically ventilated ICU patients, and should not be used in daily clinical practice to

guide nutritional support. Instead, we promote large-scale use of IC to measure REE to optimise nutritional support.

Safe enteral access

Once REE has been measured reliably and estimation of caloric targets has been made, patients on mechanical ventilation should preferably receive a nasogastric (NG) or nasojejunal (NJ) feeding tube to commence enteral nutrition (8–10). **Chapter 3** focused on evaluating enteral feeding tube placement using bedside real-time video assistance. This technique was highly successful for gastric placement, eliminating the need for X-ray confirmation. However, the technique is not suitable yet for post-pyloric feeding tube insertion.

Optimise support

Of note, the reintroduction of (par)enteral feeding after a period of fasting or starvation might induce refeeding hypophosphatemia (RH) in patients at risk (11–15). In **Chapter 4**, we reviewed the current literature about RH in critically ill patients to provide an overview of recent findings and recommendations for clinical practice. Monitoring of serum phosphate (at least once) daily during the initiation phase of nutritional support (<72 hours) is essential to observe a drop in phosphate levels induced by feeding, as no other factors can identify patients on ICU admission who will develop RH. Once diagnosed, treatment cornerstones of RH include caloric intake restriction at 500 kcal/24 hours for 48 hours, electrolyte and thiamine supplementation, correction of fluid overload and adequate glucose control (11,16,17).

In current literature, sole attention has been paid to the total energy provision; however, the effect of individual macronutrients (proteins, lipids, and carbohydrates) on clinical outcomes has yet to be studied separately in this patient group. Therefore, in **Chapter 5**, we studied the association between macronutrient intake (carbohydrates, proteins and lipids) of critically ill patients with RH and clinical outcomes. A significant association was found between protein intake during the first three days of ICU admission (the early acute phase) and 6-month mortality, in favour of the low protein intake group (≤0.71 g/kg*day), irrespective of energy intake. We hypothesise a time-dependent and dose-response relationship between protein intake and mortality in RH patients. These findings may implicate that when RH in critically ill is encountered, and thus total caloric restriction is warranted for some days, no protein supplementation should be provided during this phase.

Part II: Nutrition in the post-ICU period

The second part of this thesis focused on energy and protein intake in post-ICU convalescence. Although much research has been done during ICU stay, detailed

information about nutritional intake during the post-ICU hospitalisation period in general wards is scarce – and thus, formal guidelines about nutritional support in this period are lacking. The primary outcome of the PROSPECT-I study (PRospective Observational cohort Study of reached Protein and Energy Targets in general wards during the post-intensive care period, as reported in **Chapter 6**) was to examine daily energy and protein intake and reached targets in the post-ICU period. We demonstrated that prescribed nutritional targets were below guideline recommendations, and prescribed calories and proteins were neither ordered nor consumed. Only about half of the study participants reached >90% of prescribed protein targets overall during their post-ICU ward stay. Nutritional performance was highly dependent on the route of nutrition and was lowest among patients with oral intake only (despite food fortification strategies and/or oral nutritional supplements). The best intake was observed in patients receiving (supplemental) enteral nutrition (EN); all met >90% of their protein targets. In most cases, EN was terminated due to (supposed) sufficient energy and protein intake. However, about a third of these patients had an overall median protein adequacy of <90% before discontinuation. Moreover, discontinuing enteral nutrition resulted in immediate marked drops in energy and protein intake. Subsequently, patients needed up to six days to reach protein targets again. Our findings stress the need for follow-up studies to close the gap with individualized nutritional support in the post-ICU period to reach protein and energy targets. We suggest monitoring intake (from all nutritional routes) daily and only stopping EN when oral intake has proven to be sufficient. Subsequently, intake should be supported with food fortification or ONS, possibly even prolonged after hospital discharge, to facilitate recovery. When targets are not reached after cessation of EN, reintroduction of EN should be considered in selected cases.

Part III: Mitochondrial function in critical illness

In the third part of this thesis, we studied changes in mitochondrial function during sepsis and the association between clinical outcomes and sedative medication, which *in vitro* suppresses mitochondrial function.

During the early stages of sepsis, alterations in mitochondrial function have been observed in various cells, a combination of direct mitochondrial damage and an adaptive mitochondrial hibernation-like state response (bio-energetic downregulation) (18–23). The degree of mitochondrial inhibition has been associated with the severity of sepsis and clinical outcomes, such as mortality, although studies investigating the progression of function over time are limited (24,25). However, the findings of the Mitochondriën Intensive Care (MIC) study, as described in **Chapter 7**, argue against bio-energetic downregulation in septic peripheral blood mononuclear cells (PBMCs) during the first week of ICU admission. Instead, septic patients demonstrated higher basal and ATP-linked respiration within the first 48 hours of ICU admission than their matched

controls. In addition, a progressive increase in mitochondrial respiration during the first week was associated with 3-month mortality. Notably, PBMCs are important cells during inflammation and systemic infection. They may have a different metabolic response to sepsis compared to other tissues directly involved in multiorgan failure, such as the liver and muscle (18). Therefore, these findings cannot be generalised to model mitochondrial function in sepsis in other tissues.

Hypothetically, the sepsis-induced bioenergetic downregulation, observed in other tissue types than PBMCs, may be worsened by iatrogenic mitochondrial dysfunction, aggravating multiple organ failure and thus influencing clinical outcomes. As such, experimental *in vitro* studies have shown that propofol disturbs free fatty acid oxidation and interferes with the activity of the electron transport chain complexes (26–31). Given these results, propofol may negatively impact clinical outcomes, such as mortality and ICU-AW (as reflected by the need for a tracheostomy to wean from mechanical ventilation and discharge destinations). However, we found no statistically significant association between prolonged propofol administration and 6-month mortality and other secondary outcomes, including duration of mechanical ventilation and need for a tracheostomy to wean from mechanical ventilation, ICU and hospital LOS, discharge destinations, and ICU, in-hospital, and 3-month mortality (**Chapter 8**). Therefore, prolonged sedation with propofol, guided by RASS scores and sedation interruptions, appears safe in the least sick (as evaluated by clinical staff) critically ill adult patients who require mechanical ventilation for at least seven days. Propofol is unlikely to significantly impact mitochondrial function, translating into adverse effects on clinically relevant endpoints in these patients.

References

1. Wischmeyer PE. Are we creating survivors…or victims in critical care? Delivering targeted nutrition to improve outcomes. Curr Opin Crit Care. 2016;22(4):279–84.
2. Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma. Crit Care Med. 1999;27(7):1295–302.
3. Preiser JC, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015 Jan 29;19(1):35.
4. Lambell KJ, Tatucu-Babet OA, Chapple LA, Gantner D, Ridley EJ. Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care. 2020 Feb 4;24(1):35.
5. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care. 2019 Nov 21;23(1):368.
6. De Waele E, Spapen H, Honoré PM, Mattens S, Van Gorp V, Diltoer M, et al. Introducing a new generation indirect calorimeter for estimating energy requirements in adult intensive care unit patients: Feasibility, practical considerations, and comparison with a mathematical equation. J Crit Care. 2013;28(5):884.e1-884.e6.
7. Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clinical Nutrition. 2017;36(3):651–62.
8. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. Journal of Parenteral and Enteral Nutrition. 2016;40(2):159–211.
9. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clinical Nutrition. 2019;38(1):48–79.
10. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. Journal of Parenteral and Enteral Nutrition. 2003;27(5):355–73.
11. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clinical Nutrition. 2018;37(5):1609–17.
12. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013 Jan 11;3(1):e002173.
13. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008 Jun 28;336(7659):1495–8.
14. Kraft MD, Btaiche IF, Sacks GS. Review of the Refeeding Syndrome. Nutrition in Clinical Practice. 2005;20(6):625–33.
15. Crook MA, Hally V, Panteli J V. The importance of the refeeding syndrome. Nutrition. 2001;17(7–8):632–7.
16. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3(12):943–52.
17. Boot R, Koekkoek KWAC, van Zanten ARH. Refeeding syndrome: relevance for the critically ill patient. Curr Opin Crit Care. 2018;24(4):235–40.

18. Garrabou G, Morén C, López S, Tobías E, Cardellach F, Miró Ò, et al. The Effects of Sepsis on Mitochondria. J Infect Dis. 2011;205(3):392–400.
19. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. Physiol Rev. 2015 Jul;95(3):1025–109.
20. Thiessen SE, Van den Berghe G, Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2017;1863(10):2534–45.
21. Singer M. The role of mitochondrial dysfunction in sepsis-induced multiorgan failure. Virulence. 2013/11/01. 2014 Jan 1;5(1):66–72.
22. Brealey D, Karyampudi S, Jacques TS, Novelli M, Stidwill R, Taylor V, et al. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2004;286(3):R491–7.
23. McClave SA, Wischmeyer PE, Miller KR, van Zanten ARH. Mitochondrial Dysfunction in Critical Illness: Implications for Nutritional Therapy. Curr Nutr Rep. 2019;8(4):363–73.
24. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. The Lancet. 2002;360(9328):219–23.
25. Gründler K, Angstwurm M, Hilge R, Baumann P, Annecke T, Crispin A, et al. Platelet mitochondrial membrane depolarisation reflects disease severity in patients with sepsis and correlates with clinical outcome. Crit Care. 2014 Feb 12;18(1):R31–R31.
26. Branca D, Roberti MS, Lorenzin P, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol on the oxidative phosphorylation of isolated rat liver mitochondria. Biochem Pharmacol. 1991;42(1):87–90.
27. Branca D, Roberti MS, Vincenti E, Scutari G. Uncoupling effect of the general anesthetic 2,6-diisopropylphenol in isolated rat liver mitochondria. Arch Biochem Biophys. 1991;290(2):517–21.
28. Branca D, Vincenti E, Scutari G. Influence of the anesthetic 2,6-diisopropylphenol (propofol) on isolated rat heart mitochondria. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 1995;110(1):41–5.
29. Rigoulet M, Devin A, Avéret N, Vandais B, Guérin B. Mechanisms of Inhibition and Uncoupling of Respiration in Isolated Rat Liver Mitochondria by the General Anesthetic 2,6-Diisopropylphenol. Eur J Biochem. 1996;241(1):280–5.
30. Fedorov A, Lehto A, Klein J. Inhibition of mitochondrial respiration by general anesthetic drugs. Naunyn Schmiedebergs Arch Pharmacol. 2022/11/17. 2023 Feb 17;396(2):375–81.
31. Krajčová A, Løvsletten NG, Waldauf P, Frič V, Elkalaf M, Urban T, et al. Effects of Propofol on Cellular Bioenergetics in Human Skeletal Muscle Cells. Crit Care Med. 2018;46(3):e206–12.

Nederlandse samenvatting

Vroeger werd (sonde- of parenterale) voeding voor ernstig zieke patiënten op de Intensive care (IC) simpelweg gezien als vervanging van de orale inname. Door de loop van de jaren heen heeft dit zich echter ontwikkeld naar voedingstherapie, waarbij adequate voeding (idealiter) ingezet wordt om de katabole toestand - met een verhoogde afbraak van spiereiwitten - van ernstig zieke patiënten te reduceren, met als uiteindelijk doel het verbeteren van klinische uitkomsten op de korte en lange termijn. Er is steeds meer bewijs voor tijd- en dosisafhankelijke (en dus individueel op de patiënt afgestemde) voeding – er bestaat niet zoiets als "*one size fits all*". Ernstig zieke patiënten krijgen bij voorkeur voedingsondersteuning die aansluit bij hun metabolische behoeften, zowel op als na hun opname op de Intensive care. Dit is echter complex omdat de behoefte aan calorieën en macronutriënten (zoals eiwitten) van patiënten aanzienlijk varieert tijdens hun opname op en na de IC; formele richtlijnen voor hun dynamische voedingsdoelen ontbreken dan ook.

Het doel van dit proefschrift was het vergroten van kennis met betrekking tot optimale (gepersonaliseerde) voedingszorg voor volwassen patiënten op de Intensive Care (IC) in de verschillende fases van hun ziekte - vanaf IC-opname tot aan ziekenhuis ontslag, met als uiteindelijk streven het verbeteren van de huidige voedingsstrategieën en het voorkomen van nadelige effecten. Hieronder volgt een samenvatting van de belangrijkste bevindingen die in deze thesis zijn beschreven.

Deel I: Voeding op de Intensive Care

In het eerste deel beschrijven we enkele strategieën om voeding gedurende de IC-opname te optimaliseren: het makkelijker bepalen van energiebehoeften, het veiliger inbrengen van voedingssondes en het individualiseren van de voeding(svoorschriften) bij patiënten met *refeeding* hypofosfatemie (RH).

Het meten van de voedingsbehoeften

De energie- en macronutriëntenbehoeften (zoals eiwitten) van IC-patiënten variëren aanzienlijk gedurende de opname (1-4). Zowel onder- als overvoeding van IC-patiënten wordt geassocieerd met slechtere uitkomsten. Daarom wordt een stapsgewijze opbouw van calorieën en eiwitten gedurende de verschillen fases van ziek-zijn en herstel aanbevolen, gebaseerd op metingen van het energieverbruik in rust (rustmetabolisme) door middel van indirecte calorimetrie (5). Indirecte calorimetrie is echter in veel ziekenhuizen niet beschikbaar vanwege de kosten of het gebruiksongemak, zoals tijdrovende kalibratieprocedures (6,7). Nieuwe, gebruiksvriendelijke meetapparatuur kunnen dit probleem mogelijk oplossen. In **Hoofdstuk 2** hebben we een nieuwe

indirecte calorimeter (Beacon Care system) vergeleken met het huidige apparaat op onze IC (Deltatrac Metabolic Monitor) en daarna met verschillende voorspelmodellen. In vergelijking met de Deltatrac Metabolic Monitor kon het Beacon Care systeem de energiebehoefte in rust van beademde IC-patiënten nauwkeurig bepalen. De voorspelmodellen, daarentegen, waren slecht in staat om een schatting te geven van het energieverbruik in rust in vergelijking met beide apparaten. Deze modellen onderschatten de energiebehoeften van beademde IC-patiënten en worden daarom afgeraden voor de dagelijkse praktijk op de Intensive care. In plaats daarvan pleiten we voor grootschalig gebruik van indirecte calorimetrie om het energieverbruik in rust te meten, en op basis van die resultaten energie- en macronutriëntentoediening van IC-patiënten te optimaliseren.

Het veilig inbrengen van sondes

Alle beademde patiënten op de IC krijgen een neusmaag of neus-duodenum sonde voor het toedienen van sondevoeding (8-10). Na het inbrengen moet altijd gecontroleerd worden of het uiteinde van de sonde wel op de juist plaats ligt, en niet bijvoorbeeld in de maag. **Hoofdstuk 3** richtte zich op het evalueren van de plaatsing van nieuwe voedingssondes met behulp van realtime camerabeelden. Deze techniek was zeer succesvol voor het plaatsen van neusmaagsondes, waardoor het niet meer nodig is om een controlefoto te maken. Deze nieuwe sondes zijn echter (nog) niet geschikt voor het plaatsen van neus-duodenumsondes.

Het optimaliseren van voeding bij patiënten met refeeding hypofosfatemie

Het starten van sondevoeding of parenterale voeding na een periode van slechte voedingsinname of vasten kan in een bepaalde groep patiënten leiden tot het zogeheten *refeeding syndrome* (11-15). Een kenmerk hiervan is een laag fosfaatgehalte in het bloed (serumfosfaat); daarom wordt deze aandoening ook wel *refeeding* hypofosfatemie (RH) genoemd. In **Hoofdstuk 4** geven we een overzicht van recente onderzoeksresultaten en aanbevelingen voor IC-patiënten met (verdenking op) RH. Het controleren van het serumfosfaat (minimaal één keer per dag) in de eerste 72 uur nadat gestart is met voeding is essentieel om RH tijdig te herkennen. Als er eenmaal RH is vastgesteld, moet de calorische inname gedurende 48 uur worden beperkt tot 500 kcal/dag, naast het suppleren van elektrolyten en thiamine, het corrigeren van teveel vocht en adequate glucosecontrole (11,16,17).

In huidige literatuur wordt uitsluitend aandacht besteed aan de totale calorische voedingsinname in deze patiëntengroep. Het effect van individuele macronutriënten (eiwitten, vetten en koolhydraten) op klinische uitkomsten hebben we in **Hoofdstuk 5** bestudeerd. Hierbij hebben we significante associatie gevonden tussen eiwitinname tijdens de eerste drie dagen van het verblijf op de IC (de vroege acute fase) en de

6-maanden mortaliteit. De groep met een lage eiwitinname (≤0,71 g/kg*dag) liet de gunstigste uitkomst zien, ongeacht de energie-inname. We veronderstellen een tijds- en dosisafhankelijke relatie tussen eiwitinname en sterfte bij RH-patiënten. Dit impliceert dat, wanneer RH is vastgesteld en de totale calorische voedingsinname voor enkele dagen beperkt wordt, er in die fase geen extra eiwitsupplementen gegeven moeten worden.

Deel II: Voeding in de post-IC periode

Het tweede deel van deze thesis richtte zich op energie- en eiwitinname tijdens de herstelperiode na de IC (post-IC fase) op de verpleegafdelingen. Hoewel er veel voedingsonderzoek gedaan wordt en is tijdens IC-opname, is gedetailleerde informatie over de voedingsinname tijdens de post-IC fase schaars – er zijn dan ook geen formele voedingsrichtlijnen voor deze periode. Het doel van de PROSPECT-I studie (PRospectieve Observationele cohortstudie van bereikte Eiwit- en Energie-doelen op de verpleegafdelingen tijdens de post-intensive care periode, zoals beschreven in **Hoofdstuk 6**) was het onderzoeken van de dagelijkse energie- en eiwitinname en het bereiken van voedingsdoelen in de post-IC periode. We hebben aangetoond dat slechts ongeveer de helft van geïncludeerde patiënten >90% van de voorgeschreven eiwitdoelen haalde tijdens hun verblijf op de afdeling na IC-ontslag.

Het al dan niet behalen van de gestelde voedingsdoelen bleek sterk afhankelijk van het type voedingsinname. Patiënten met alleen orale voedingsinname (ondanks supplementen) behaalden minder frequent hun voedingsdoelen. Patiënten met (aanvullende) sondevoeding daarentegen, bereikten allemaal >90% van hun eiwitdoelen. De belangrijkste reden om sondevoeding te staken was (vermeende) voldoende inname van calorieën en eiwitten.

Echter, meer een derde van deze patiënten had een eiwitinname <90% van het gestelde doel. Bovendien resulteerde het staken van sondevoeding meteen in aanzienlijke dalingen van de energie- en eiwitinname. Patiënten hadden bijna een week (tot zes dagen) nodig om opnieuw hun eiwitdoelen te halen.

Onze bevindingen benadrukken de noodzaak voor vervolgstudies om de kloof te dichten met geïndividualiseerde voedingsadviezen om eiwit- en energiedoelen te bereiken in de post-IC periode. We stellen voor om de voedingsinname (zowel oraal, via sonde- en parenterale voeding) dagelijks te monitoren en sondevoeding alleen te stoppen wanneer de orale voedingsinname voldoende is. Wanneer de voedingsdoelen niet worden bereikt na het staken van sondevoeding, zou het hervatten daarvan in bepaalde situaties overwogen moeten worden.

Deel III: Mitochondriële functie in ernstig zieke patiënten

In het derde deel van deze thesis hebben we veranderingen in de mitochondriële functie in perifere mononucleaire bloedcellen (PBMCs) tijdens sepsis bestudeerd en de associatie tussen het toedienen van slaapmedicatie (met in-vitro een verandering in mitochondriële functie) en klinische uitkomsten.

Mitochondriële veranderingen

In eerdere studies zijn tijdens de vroege stadia van sepsis veranderingen in de mitochondriële functie waargenomen. Deze veranderingen zijn een combinatie van directe mitochondriële schade en een adaptieve mitochondriële hibernatie-achtige respons (bio-energetische downregulatie). De mate van mitochondriële downregulatie is geassocieerd met de ernst van de sepsis en klinische uitkomsten zoals sterfte, alhoewel studies die de veranderingen in functie over verloop van tijd bestuderen schaars zijn.

De bevindingen van de Mitochondriën Intensive Care (MIC) studie, zoals beschreven in **Hoofdstuk 7**, pleiten echter tegen bio-energetische downregulatie in PBMCs van septische patiënten tijdens de eerste week van hun IC-opname. In plaats daarvan werd een hogere basale en ATP-linked respiratie gezien tijdens de eerste 48 uur van IC-opname in vergelijking met hun gematchte controlepersonen. Deze verhoogde respiratie bleek geassocieerd met een verhoogde 3-maanden mortaliteit. Echter, aangezien PBMCs belangrijke cellen in de onstekingsrespons zijn, kunnen deze resultaten niet gegeneraliseerd worden om uitspraken te doen over mitochondriële functie tijdens sepsis in andere typen weefsels.

De bio-energetische downregulatie die in andere weefseltypen wordt waargenomen, kan hypothetisch gezien verergerd worden door toegediende medicatie met een negatief effect op mitochondriële functie. Een veelvuldig toegediend intraveneus sedativum met invloed op mitochondriële functie is propofol: experimentele in vitro studies hebben aangetoond dat dit slaapmiddel de oxidatie van vrije vetzuren verstoort en de elektronentransportketen beïnvloedt. Theoretisch gezien, zou propofol daarom een negatieve invloed kunnen hebben op klinische uitkomsten, zoals een verhoogde mortaliteit en toegenomen IC-verworven spierzwakte (*ICU-acquired weakness*, ICU-AW). In **Hoofdstuk 8** vonden we echter geen statistisch significante associatie tussen langdurige toediening van propofol en de 6-maanden mortaliteit en andere secundaire uitkomsten, waaronder beademingsduur en de noodzaak voor een tracheostomie, IC- en ziekenhuisverblijfsduur, ontslagbestemmingen, en de sterfte op de IC, in het ziekenhuis en na drie maanden. Daarom lijkt langdurige sedatie met propofol van (de minst zieke) volwassen beademde patiënten gedurende minimaal 7 dagen aan de hand van RASS-scores en dagelijkse *wake up calls*, veilig te zijn.

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About the author

Rianne Slingerland-Boot was born on the 2nd of January 1993 in Ede, The Netherlands. She graduated from secondary school in 2011, after which she studied medicine at the University of Utrecht. The last year of her medical training focused on acute care medicine. During her research project at the department of Trauma Surgery, which resulted in two publications, she gained interest in science. She completed this dedicated study year with an elective internship in the Intensive care unit (ICU) department of Gelderse Vallei hospital (Ede). Rianne started working as a resident in this ICU after her graduation from medical school (*cum laude*) in 2017. One year later, in 2018, she was appointed as a PhD candidate in collaboration with Wageningen University & Research, division of Human Nutrition & Health. During the research which is described in this thesis, she initially continued working as an ICU resident, but switched in 2020 to Internal Medicine (Alrijne Ziekenhuis in Leiden/Leiderdorp and Franciscus Gasthuis & Vlietland in Rotterdam / Schiedam successively). Currently, Rianne is a general practitioner in training.

List of publications

Articles in this thesis

Boot R, Koekkoek KWAC, van Zanten ARH. Refeeding syndrome: relevance for the critically ill patient. Curr Opin Crit Care. 2018 Aug;24(4):235-240.

Slingerland-Boot R, Bouw-Ruiter M, van Manen C, Arbous S, van Zanten A. Video-assisted placement of enteral feeding tubes using the Integrated Real-Time Imaging System (IRIS)-technology in critically ill patients. Clin Nutr. 2021 Aug;40(8):5000-5007.

Slingerland-Boot H, Adhikari S, Mensink MR, van Zanten ARH. Comparison of the Beacon and Quark indirect calorimetry devices to measure resting energy expenditure in ventilated ICU patients. Clin Nutr ESPEN. 2022 Apr;48:370-377.

Slingerland-Boot R, van der Heijden I, Schouten N, Driessen L, Meijer S, Mensink M, van Zanten A. Prospective observational cohort study of reached protein and energy targets in general wards during the post-intensive care period: The PROSPECT-I study. Clin Nutr. 2022 Oct;41(10):2124-2134.

Slingerland-Boot R, Rooijakkers E, Koekkoek K, van Blokland D, Arbous S, van Zanten A. Macronutrient intake and outcomes of ICU patients with refeeding hypophosphatemia. Clin Nutr ESPEN. 2023 Jun;55:191-199.

Slingerland-Boot R, Kummerow M, Arbous SM, van Zanten ARH. Association between first-week propofol administration and long-term outcomes of critically ill mechanically ventilated patients: A retrospective cohort study. Clin Nutr. 2024 Jan;43(1):42-51.

Moonen HPFX[#], **Slingerland-Boot H[#]**, de Jong JCBC, Nieuwenhuizen AG, Grefte S, van Zanten ARH. The progress of mitochondrial function during the initial and late acute phases of sepsis in ICU patients. *Submitted for publication.*

Other articles

Moonen HPFX, van Zanten FJL, Driessen L, de Smet V, **Slingerland-Boot R**, Mensink M, van Zanten ARH. Association of bioelectric impedance analysis body composition and disease severity in COVID-19 hospital ward and ICU patients: The BIAC-19 study. Clin Nutr. 2021 Apr;40(4):2328-2336.

Karhof S[#], **Boot R**[#], Simmermacher RKJ, van Wessem KJP, Leenen LPH, Hietbrink F. Timing of repair and mesh use in traumatic abdominal wall defects: a systematic review and meta-analysis of current literature. World J Emerg Surg. 2019 Dec 17;14:59.

Karhof S, Hietbrink F, **Boot R**, van Wessem KJP, Leenen LPH, Simmermacher RKJ. Management strategies and outcome of blunt traumatic abdominal wall defects: a single centre experience. Injury. 2019 Sep;50(9):1516-1521.

Boot H, Savelkoul C, Tjan DHT. Een vrouw met koorts en een pijnlijke heup [A woman with fever and a painful hip]. Ned Tijdschr Geneeskd. 2018 Jun 22;162:D2260.

[#] *contributed equally to this publication.*

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