Clinical Nutrition ESPEN 43 (2021) 383–389

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Energy expenditure and feeding practices and tolerance during the acute and late phase of critically ill COVID-19 patients

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ARTICLE INFO

Article history:
Received 19 March 2021
Accepted 22 March 2021

Keywords:
Resting energy expenditure
COVID-19
Critically ill
Enteral nutrition

SUMMARY

Background & aims: Different metabolic phases can be distinguished in critical illness, which influences nutritional treatment. Achieving optimal nutritional treatment during these phases in critically ill patients is challenging. COVID-19 patients seem particularly difficult to feed due to gastrointestinal problems. Our aim was to describe measured resting energy expenditure (mREE) and feeding practices and tolerance during the acute and late phases of critical illness in COVID-19 patients.
Methods: Observational study including critically ill mechanically ventilated adult COVID-19 patients. Indirect calorimetry (Q-NRG+, Cosmed) was used to determine mREE during the acute (day 0–7) and late phase (>day 7) of critical illness. Data on nutritional intake, feeding tolerance and urinary nitrogen loss were collected simultaneously. A paired sample t-test was performed for mREE in both phases.
Results: We enrolled 21 patients with a median age of 59 years [44–66], 67% male and median BMI of 31.5 kg/m^2 [25.7–37.8]. Patients were predominantly fed with EN in both phases. No significant difference in mREE was observed between phases ($p = 0.529$). Sixty-five percent of the patients were hypermetabolic in both phases. Median delivery of energy as percentage of mREE was higher in the late phase (94%) compared to the acute phase (70%) ($p = 0.001$). Urinary nitrogen losses were significant higher in the late phase ($p = 0.003$).
Conclusion: In both the acute and late phase, the majority of the patients were hypermetabolic and fed enterally. In the acute phase patients were fed hypocaloric whereas in the late phase this was almost normocaloric, conform ESPEN guidelines. No significant difference in mREE was observed between phases. Hypermetabolism in both phases in conjunction with an increasing loss of urinary nitrogen may indicate that COVID-19 patients remain in a prolonged acute, catabolic phase.

1. Introduction

A new strain of coronavirus SARS-CoV-2 (COVID-19) has been identified as the cause of the pandemic outbreak of respiratory illness in people [1]. People who are infected with the virus experience symptoms of fever, cough, nasal congestion, fatigue and a hyper inflammatory reaction can occur resulting in a systematic response and multiple organ failure (MOF) [2]. Besides this, the virus may invade the gastrointestinal tract [3]. Elderly people (>60 years) and those with comorbidities are more likely to become critically ill and be admitted to an intensive care unit (ICU) for treatment of COVID-19 induced pneumonia [1,4,5].

Providing optimal nutritional intake is a challenge in critically ill patients due to a complex and fluctuating metabolism that affects their nutritional status over time. Critical illness is characterized by an inflammatory response, which incites a catabolic response, and can be divided into several metabolic disease phases [6,7]. The 'early acute phase' is seen during the first 48 h after ICU admission

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https://doi.org/10.1016/j.clnesp.2021.03.019

and will subsequently evolve into the 'late acute phase', usually lasting no longer than day seven of admission. During the acute phase the body is provided with energy from an irrepressible endogenous supply of glucose through gluconeogenesis, covering over 50% of resting energy expenditure (REE) [8–10]. In critically ill COVID-19 patients, the acute phase is clinically characterized by a severe inflammatory response [4]. It has been shown that the acute inflammatory reactions increases REE, but underlying conditions such as MOF, use of sedatives and paralyzing agents decreases REE [11,12]. Following the acute phase, the patient enters the 'late (or chronic) phase' of disease, which evolves into the 'recovery phase' after leaving the ICU, generally associated with an increase in REE [10,13,14]. In COVID-19 patients, the late phase is characterized by a lower use of sedatives, as well as initiation of weaning off mechanical ventilation and starting mobilization parallel with a reduction of inflammation. However, COVID-19 patients are admitted to the ICU for a prolonged period in comparison to regular ICU patients [4], thus the metabolic phases of disease may be different and longer than usual.

Predictive equations for calculating energy requirements (pREE), often used in day-to-day clinical practice, are inaccurate for the ICU population when compared to indirect calorimetry [9,15]. Indirect calorimetry is considered the golden standard to determine measured REE (mREE) of critically ill patients [7,16]. Accurate determination of caloric needs for ICU patients is of importance to prevent both overfeeding and underfeeding [7,17], as overfeeding is related to a higher risk on mortality [18] and underfeeding negatively impacts ICU stay, infections, muscle mass and time spent on mechanical ventilation [7,19,20]. Regardless of these challenges, patients admitted with COVID-19 also seem particularly difficult to feed enterally, with diarrhea and high gastric residual volumes (GRV) recorded by clinicians. Faeces volumes over 350 g per day are associated with malabsorption [21], whereas a large GRV (2× >150 ml in 24 h) is more indicative of delayed gastric emptying [22–24].

So far, there is literature on the time course of mREE during different metabolic phases and conditions and diseases [13,14,25–31], but little is known about this in COVID-19 patients [32,33]. Furthermore, no data are available yet on feeding practices and tolerance for COVID-19 patients. Therefore, the aim of this study is to describe mREE and feeding practices and tolerance during the acute and late phases of critical illness in COVID-19 patients. Based on the clinical characterization of these patients we hypothesized a lower mREE in the acute phase compared to pREE and an increase in mREE in the late phase. Furthermore, feeding intolerance in both phases was expected.

2. Material and methods

2.1. Study population and study design

This single-centre observational study was conducted from April 2020 till July 2020 in the ICU of the Erasmus Medical Centre (MC), with the approval from the institutional review board of the Erasmus MC, Rotterdam, The Netherlands (MEC-2020-0336). The study protocol adheres to the current standard of care feeding protocol of the Department of Intensive Care. The need for informed consent was waived by the Institutional review board. All adult patients (≥18 years of age) admitted to the ICU with a confirmed COVID-19 respiratory infection were included. Patients with 1) metabolic disease requiring a specific diet (e.g. Phenylketonuria), 2) (home)-parenteral nutrition started >7 days before admission unrelated to COVID-19 infection, 3) no indirect calorimetry measurement in both acute and late phase, were excluded.

2.2. Data collection and management

Data were collected from the data management system (HiX™, Chipsoft, Amsterdam, The Netherlands). From each COVID-19 patient mREE was measured once during the acute phase (lasting up until day 7), and once during the late phase (from day 8 onwards) [7]. Patients transferred from other ICU's were considered to be in the acute or late phase, according to their admission day to the ICU of the Erasmus MC. Since the most critically ill patients were transferred, we considered them all to be in the acute phase upon admission. Patient's baseline characteristics included demographic data (age, weight, height, sex, Body Mass Index (BMI), Mortality risk score (APACHE-IV) score and comorbidities). Additional variables collection of additional variables pertained to the same day as mREE was measured were collected and included clinical data in relation to mREE; body temperature, illness severity score (SOFA-score), gradation of sedation depth (RASS-score), plasma inflammatory markers (C-reactive protein (CRP), Interleukin-6 (IL-6)), use of opiates (sufentanil, remifentanil) and type of mechanical ventilation (pressure controlled, pressure support), urinary urea levels, gastrointestinal function (based on GRV and faeces volume) and nutritional data (oral, EN or PN intake, type of feeding tube, caloric and protein intake, non-nutritional calories, calculated feeding goal (CFG) and prescribed feeding goal).

2.2.1. Energy expenditure

mREE was determined with an indirect calorimeter (Q-NRG+, Cosmed, Italy) and performed preferably on day 4 and 10 of ICU admission. Prior to each measurement patients had to be in a clinically stable condition for at least 30 min and FiO_2 <70%. The Q-NRG+ was connected to the ventilator conform the practical guidance for the use of indirect calorimetry in COVID-19 patients [34]. Duration of the measurement was minimum 10 min during steady state (<10% coefficient of variation of VCO2 and VO2). Oxygen consumption, carbon dioxide production, the respiratory quotient (RQ) and mREE were collected. Valid measurements were defined as RQ ranges between 0.7 and 1.1 and <10% overall variation of VCO2 and VO2. Hypermetabolism was defined as mREE/pREE >1.1 and hypometabolism as <0.9. All measurements were performed by the same person (BVH).

2.2.2. Feeding practice and tolerance

Data on feeding practices and tolerance were collected at the day mREE was performed. Feeding practice includes oral, enteral or parenteral feeding administration and place of feeding tube (e.g. nasogastric, nasoduodenal). GRV and faeces volumes were considered as indicators for feeding intolerance. GRV was considered high if ≥2 times ≥150 mL per day (conform standard feeding protocol in our hospital). Malabsorption was defined as faeces volumes ≥350 g per day [21]. Additionally, urine samples were collected to determine urea levels (mmol/L). Urine nitrogen loss (g/d) was calculated from urea levels and 24-h urine volumes at the day the sample were taken. Urinary urea was not determined for patients who received continuous renal replacement therapy (CRRT) [35,36]. Urinary protein loss (g/d) was calculated as urinary nitrogen loss × 6.25. Protein balance (g/d) was defined as delivered protein intake minus the urinary protein loss.

2.2.3. Nutritional intake

Nutritional parameters included administered nutritional energy (kcal) and protein (grams) and non-nutritional calories (e.g. lipid-based emulsions and glucose) intake per day. Feeding goals, as recommended by ESPEN, were determined per individual by one ICU dietitian (PLL) [7]. The initial goal was to achieve hypocaloric (<70% of mREE) energy provision in the acute phase and

normocaloric (70–100% of mREE) in the late phase. Conform our nutrition protocol actual body weight (kg) upon admission was used to calculate feeding goals, unless there was clinical manifestation of fluid overload, the estimated usual body weight before admission was used. The calculated feeding goal (CFG) for energy, equal to pREE, was determined for every patient individually per time point. The CFG corresponds with the energy requirement as predicted with the use of either the WHO (BMI $\leq$ 30 kg/m^2) or Harris and Benedict (BMI > 30 kg/m^2) equation [37–39]. Correction of energy requirement for influential factors (+0–10% sedation and mechanical ventilation, +10–20% mechanical ventilation, +20–30% no mechanical ventilation), were made per individual for the day indirect calorimetry was performed and ranged generally from 0 to 30 percent. The CFG for protein generally ranging from 1.3 to 1.7 g/kg [7,40], taking into account the presence of wounds/decubitus and CRRT [7,40]. Delivery of energy was calculated by adding all calories from oral intake, EN, PN and non-nutritional sources. Delivery of protein was calculated by adding protein administered by oral intake, EN and PN.

2.3. Statistical analysis

Data on baseline characteristics were analyzed by means of descriptive statistics: mean (standard deviation (SD)), median (interquartile range (IQR)) and numbers (percentages (%)). Differences between pREE and mREE within each phase and differences in mREE between the acute and late phase were analyzed with a paired samples t-test. Data analysis was performed using IBM SPSS statistics for windows, version 25.0 (IBM Corp. Armonk, NY, USA). A 2-sided p-value of less than $\alpha = 0.05$, was considered to be statistically significant.

3. Results

3.1. Study population

After METC approval a total of 62 critically ill patients with confirmed COVID-19 were eligible for enrollment. Of which 21 patients (67% male) were measured in both phases (Table 1). The majority of the excluded patients had only one measurement or were measured outside the set time frame of our predefined disease phases. The median age of patients was 59 years [44–66], median BMI was 31.5 kg/m^2 [25.7–37.8] and 57% were obese (BMI > 30 kg/m^2). The most common comorbidities were diabetes mellitus type 2, cardiac disease and respiratory disease (Table 1), and the majority of the patients had at least two comorbidities. Most patients (90.5%) were transitioned from other ICU's to the ICU in the Erasmus MC, an academic, tertiary referral centre specialized in mechanical ventilation. The median of days spend in another ICU was 3 days [0–6]. A total of 33% patients was measured in the acute early and 67% in the acute late phase, which was considered to be the acute phase.

Table 1
Baseline characteristics of study population at admission to the ICU.

	All included patients, n = 21
Male sex, n (%)	14 (66.7)
Age (yr), median [IQR]	59 [44–66]
BMI (kg/m^2), median [IQR]	31.5 [25.7–37.8]
Normal weight, n (%)	5 (23.8)
Overweight, n (%)	4 (19.0)
Obese, n (%)	12 (57.1)
APACHE IV score (%), median [IQR]	22.2 [9.5–35.0]
Comorbidities, n (%)	
Diabetes mellitus type 2	10 (35.5)
Cardiac disease	5 (23.8)
Respiratory disease	8 (38.1)
Gastrointestinal disease	1 (4.8)
Cancer	2 (9.5)
Renal disease	2 (9.5)
Immune disease	1 (4.8)
Neurological disease	1 (4.8)
Syndrome[a]	1 (4.8)
Transferred from another ICU, n (%)	19 (90.5)

Abbreviations: APACHE IV = acute physiology and chronic health evaluation IV, BMI = body mass index, ICU = intensive care unit. APACHE IV is expressed as a risk percentage ranging from 0 to 100%, where a higher percentage indicates higher risk on mortality at admission.
[a] Syndrome due to a genetic disorder.

3.2. Feeding practice and tolerance

Patients were predominantly fed with EN in both phases. One patient received PN in the late phase. Nasoduodenal tubes were used more often in the late phase (71%) as opposed to the acute phase (48%) (p = 0.021). Presence of gastro-intestinal symptoms differed between phases. A higher median GRV (ml/day) was recorded in the acute phase (125 [26–350]) compared to the late phase (75 [40–238]). In the late phase, a higher frequency of malabsorption (45%) was seen, compared to the acute phase (20%). Urinary nitrogen loss and urinary protein losses were significantly higher in the late phase compared to the acute phase (p = 0.003) (Table 2).

3.3. Measured resting energy expenditure

All patients were measured in both the acute and late phase, with median day of measurement, day 4 [2–5] and day 11, respectively [9–12]. Overall we found no significant difference of mREE between the acute and late phase (p = 0.529) (Table 3). However, mREE was percentual higher in the late phase for the majority of the patients (Fig. 1) and hypermetabolism was present in both phases in 65% of the patients (Table 3). Body temperature was comparable between phases. Median RASS score, CRP and IL-6 values decreased significantly from the acute to the late phase (Table 3). Ventilation mode shifted from predominantly controlled ventilation in the acute phase (90%) to mostly ventilation support in the late phase (65%). Use of opiates changed from an opiate with a long-half-life (sufentanil) in the acute phase to a short-acting opiate (remifentanil) in the late phase (Table 3). The median length of ICU stay was 29 days [16–38] and 81% of the patients survived. In total the median length of hospital stay was 38 days [18–46]. The majority of the patients (60%) received inpatient or home-based rehabilitation care due to severe muscle weakness after discharge.

3.4. Nutritional intake

The mean delivery of energy as percentage of mREE was lower in the acute phase (70%) compared to the late phase (94%) (p = 0.001). In both the acute and late phase of disease mREE was significantly higher compared to pREE (respectively p = 0.001 and p = 0.000). Concerning protein delivery, administered and prescribed amounts were higher in the late phase compared to the acute phase (Table 3). The percentage of protein delivered compared to the prescribed goal did not differ significantly (p = 0.471). Based on urinary nitrogen loss presented in Table 2, the mean urinary protein loss was 110 g (1.5 g/kg/d) in the acute and 161 g (1.9 g/kg/d) in the late phase [41]. This resulted in a significantly more negative urinary protein balance (p = 0.003) (Table 3).

Table 2
Feeding practices and tolerance, energy and protein administration during the acute phase (≤7 days) and late phase (>7 days) of critical illness for all subjects.

Feeding practice and tolerance	Acute phase[a]	Late phase[b]	p-value
	n = 21	n = 21	
EN vs. PN, n	21 vs. 0	20 vs. 1	
Feeding tube, n (%)			
Nasogastric tube	11 (52.4)	6 (28.6)	
Nasoduodenal tube	10 (47.6)	15 (71.4)	**0.021**
GRV (ml/day), median [IQR]	125 [26–350]	75 [40–238]	0.785
High GRV[c], n (%)	2 (9.5)	1 (4.8)	0.578
Metoclopramide (yes), n (%)	13 (61.9)	7 (33.3)	0.055
Faeces (ml/day), median [IQR]	0 [0–300]	270 [15–638]	0.104
Malabsorption[d] (yes), n (%)	4 (20.0)	9 (45.0)	0.227
Urinary nitrogen loss (g/d), mean ± SD	18 ± 11	26 ± 13	**0.003**
Urinary protein loss (g/d), mean ± SD	110 ± 66	161 ± 81	**0.003**
Nutritional intake			
Administered energy (kcal), mean ± SD	1560 ± 577	2126 ± 639	**0.001**
Administered protein (g/d), mean ± SD	97 ± 38	127 ± 38	**0.001**

Abbreviations: EN = enteral nutrition, GRV = gastric residual volume, mREE = measured resting energy expenditure, pREE = predicted resting energy expenditure, PN = parenteral nutrition.
p-value of less than $\alpha = 0.05$, was considered to be statistically significant.
[a] Median day of measurement: 4 [2–6].
[b] Median day of measurement: 11 [9–14].
[c] ≥2 times ≥150 mL GRV/day was considered to be high GRV.
[d] >350 g faeces/day was considered malabsorption [21]. Urinary protein loss g/d is calculated as urinary nitrogen loss g/d × 6.25.

Table 3
Measured energy and protein balance and independent variables in the acute and late phase of critical illness in patients with two mREE measurements (n = 21).

	Acute phase[a]	Late phase[b]	p-value
Energy			
pREE (kcal), mean ± SD	1900 ± 334	1975 ± 330	0.522
mREE (kcal), mean ± SD	2267 ± 668	2284 ± 623	0.529
RQ, mean ± SD	0.76 ± 0.11	0.81 ± 0.09	0.934
Metabolism[c], n (%)			
Hypometabolic	1 (5.0)	1 (5.0)	
Normometabolic	6 (30.0)	6 (30.0)	
Hypermetabolic	13 (65.0)	13 (65.0)	
Delivery of calories (% of mREE), mean ± SD	70 ± 24	94 ± 24	**0.004**
Protein			
Prescribed protein feeding goal (g), mean ± SD	108 ± 40	133 ± 25	**0.005**
Delivery of protein (g/kg/d), mean ± SD	1.0 ± 0.4	1.3 ± 0.3	0.053
Urinary protein loss (g/kg/d), median [IQR]	1.5 [0.9–1.8]	1.9 [1.3–2.3]	0.008
Urinary protein balance[d] (g/d), median [IQR]	−9.0 [−28.4; 31.8]	−63 [−101.4; −12.1]	**0.003**
Potential confounding variables			
Body temperature (°C), mean ± SD	37.6 ± 0.8	37.7 ± 1.1	0.806
RASS-score, median [IQR]	−5 [−5; −5]	−4 [−5; −2]	**0.013**
SOFA-score, median [IQR]	5 [4.5–6]	4 [2–5]	0.160
Ventilation mode, n (%)			
Controlled ventilation	19 (90.0)	7 (35.0)	
Ventilation support	2 (10.0)	13 (65.0)	
C-reactive protein (mg/L), median [IQR]	196 [132–310]	72 [29–173]	**0.001**
Interleukin-6 (pg/mL), median [IQR]	71 [45–268]	29 [9–61]	**0.006**
Urinary nitrogen loss (g/d), median [IQR]	16 [10.6–18.3]	21 [18.5–29.3]	**0.003**
Opiates, n (%)			
Sufentanil	17 (80.0)	4 (20.0)	
Remifentanil	4 (20.0)	17 (80.0)	

Abbreviations: mREE = measured resting energy expenditure, pREE = predicted resting energy expenditure, RASS = richmond agitation–sedation scale, RQ = respiratory quotient, SOFA = sequential organ failure assessment score.
p-value of less than $\alpha = 0.05$, was considered to be statistically significant.
[a] Median day of measurement: 4 [2–5].
[b] Median day of measurement: 11 [9–12].
[c] Metabolism determined as (predicted REE/mREE) × 100%. Considered hypometabolic if <90% of predicted REE and hypermetabolic if >110% of predicted REE.
[d] Urinary protein balance defined as delivered protein intake g/d − urinary protein loss g/d.

4. Discussion

This study describes the mREE, feeding practices and feeding tolerance of critically ill COVID-19 patients. No significant difference in mREE between the acute and late phase of critical illness was observed in our sample of patients. Overall, mREE was higher than pREE in both phases. Demographics of our sample size based on BMI [42–45] and gender [42,46–49] are comparable with other recent studies in critically ill COVID-19 patients.

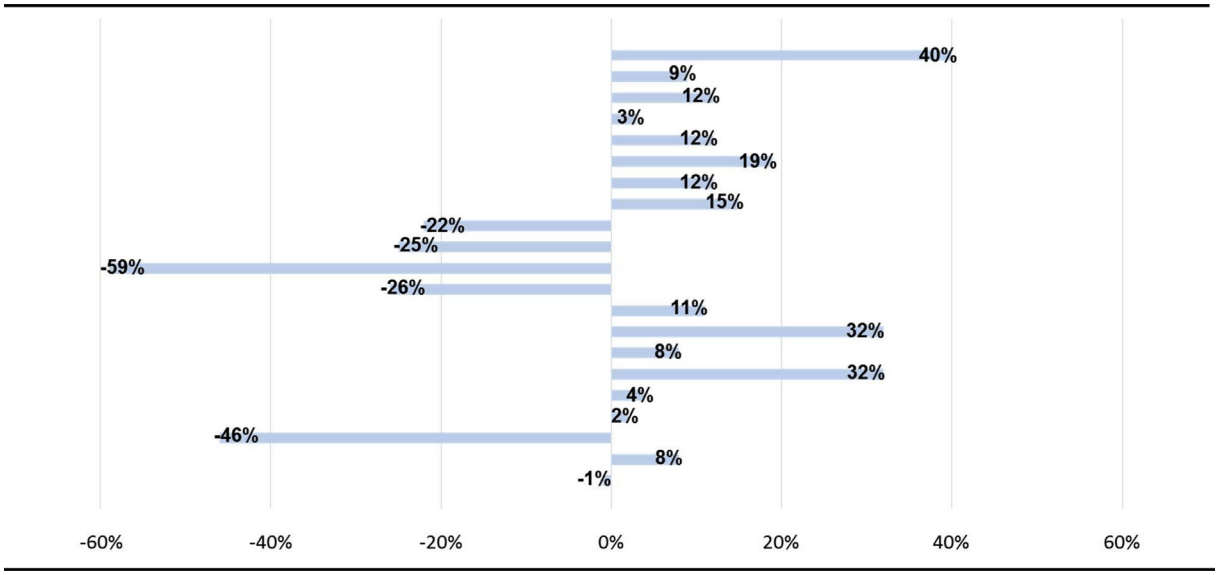

Fig. 1. Percentual change in kilocalories of measured resting energy expenditure (mREE) between the first measurement in the acute phase and the second measurement in the late phase per patient (n = 21).

Concerning feeding practices in both phases of disease enteral nutrition could be administered and increased but remained below the mREE. High GRV was not frequently observed in both phases, as the malabsorption was more frequently seen in the late phase, although this was not significant.

Contrary to our expectations we didn't find a significant difference in mREE between the phases. It might be expected that mREE is increased during the late phase of disease due to less use of sedatives and weaning of mechanical ventilation as a result of decreased inflammation. Although inflammatory parameters decreased, it might be explained by a prolonged acute phase in COVID-19 patients. It is questionable whether our measurement schedule was suitable to distinguish the phases in our study population. Furthermore, the massive loss of muscle mass during ICU stay will lead to a decrease to the contribution of mREE [10,40]. However, we didn't have measurements of muscle mass loss of these patients in both phases of disease and because the fractional contribution of muscle mass is approximately 20% of the mREE, it is questionable whether the loss of muscle mass and it's contribution in mREE can be accurately measured [50,51].

In our study hypermetabolism was present in both phases in 65% of the patients. This is in accordance with two studies in which respectively 22 and 7 COVID-19 patients was measured respectively between day 5–21, and day 8–55 after ICU admission [32,33]. In these studies all patients were hypermetabolic after day 7, however no intra-individual analysis of mREE were performed. De Waele et al. reported normometabolism in 6 COVID-19 patients at day 1–26 after ICU admission [52]. Based on our results the need for indirect calorimetry to guide nutritional treatment in COVID-19 patients should be emphasized since predictive formulas underestimated REE.

Enteral nutrition was most commonly used in both phases (100% vs. 95%), with significant more use of nasoduodenal tubes in the late phase ($p = 0.021$). Compared to mREE hypocaloric energy provision (70%) was observed in the acute phase, which seems an optimal intake during the first 3 days of ICU stay [26]. After which the caloric delivery could be increased to 80–100% of mREE [7]. The deficit in our study might be explained by interruptions of feeding due to prone positioning and medical procedures [53,54]. Supplemental parenteral nutrition in the first week of ICU stay is not a standard procedure in our protocol and is weighted case-by-case, because the best timing remains debatable [7]. During the late phase the caloric delivery was almost normocaloric (94% of mREE). Likewise, Zusman et al. investigated mREE in a general ICU population (n = 1171) and reached 90% caloric administration of mREE [26]. Protein delivery was in accordance with the ESPEN guidelines in the acute and late phase (1.0 g/kg/d vs. 1.3 g/kg/g and 1.3 g/kg/d vs. 1.3 g/kg/g) [7,55].

However, we observed a negative protein balance in both phases based on urinary protein loss which might indicate that the protein intake was inadequate to compensate the protein breakdown. Moreover, faecal and insensible nitrogen losses were not even taken into account. It has been suggested that critically ill patients with obesity, like our study population, should receive higher protein intakes of 2.0–2.5 g/ideal bodyweight kg/d to approach nitrogen equilibrium [56]. We found significant more urinary nitrogen loss in the late phase ($p = 0.003$). Lower levels in the acute phase could be the result of autophagy and a smaller extent of delivered protein in this phase. In the late phase of critical illness, the human body relies more on exogenous sources of energy and protein [6]. Moreover, the accumulated loss of muscle mass during ICU stay due to catabolism and immobilization may result in increased levels of nitrogen excretion in the late phase [57,58]. Likewise, Pittiruti et al. reported an increase of urinary nitrogen loss in the late phase (>5 days) of both septic and non-septic patients, with the highest amounts in septic patients without MOF (25.6 g/d) [59]. Long et al. reported an increase of urinary nitrogen loss following the severity of disease, without a significant difference between trauma, septic and burn patients [40]. Based on these results the need for monitoring urinary nitrogen excretion should be emphasized to guide protein delivery in COVID-19 patients. It is however questionable if a higher protein intake can be achieved to overcome this negative protein balance due to the persistent high inflammatory state of the patients.

Contrary to our expectations gastrointestinal symptoms were mild and GRV volumes remained low in both phases whereas faeces volume increased in the late phase. This might be due to the fact that the volume of enteral nutrition increased and inflammatory response decreased. This is in contrast with Arkin et al. who reported that there is a considerable gastrointestinal involvement

due to the COVID-19 infection [54]. It is contemplated that the abundant use of sedatives reduces gastrointestinal motility and it was reported that gastrointestinal hypo motility was worse in COVID-19 patients compared to other ICU patients due to the high-doses of sedatives who were needed [54,55]. However this was not observed in our study and might be explained by the fact that feeding tolerance was only measured at the day mREE was performed.

Limitations of our study are mREE was performed in the acute and late phase according to our schedule, but not corrected for the days spend in another ICU which could result in bias. Delivery of calories and protein was according to our protocol, but nutritional losses and feeding tolerance could not be fully explored due to the observational study design and depends on accurate reporting in the medical charts. Also, urinary nitrogen losses may be underestimated, due to the catabolic nature of ICU patients and the possibility of losses via other routes [60].

5. Conclusion

No significant difference in measured energy expenditure between the acute and late phase of critical illness was observed in this sample of COVID-19 patients. However, in both phases the majority of the patients were hypermetabolic and fed below mREE. In conjunction with an increasing loss of nitrogen in the late phase and a negative nitrogen balance it can be concluded that patients remained in a prolonged catabolic phase. Our sample of COVID-19 patients could be fed enterally with an acceptable tolerance of intake but it has to be investigated if it is possible to achieve a higher enteral intake without an increase of gastro-intestinal intolerance to overcome the massive protein breakdown and counteract the catabolic response.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors conceived and designed the research; PLL, BVH conducted the measurements and calculations; PLL and JMS analyzed the data; PLL and BVH wrote the manuscript. All authors have read, edited and approved the manuscript.

Declaration of competing interest

None Declared.

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