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Original article

Assessing calorie and protein recommendations for survivors of critical illness weaning from prolonged mechanical ventilation – can we find a proper balance?



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SUMMARY

Background & aims: Survivors of critical illness requiring prolonged mechanical ventilation (PMV) are predisposed to malnutrition, muscle wasting, and weakness. There is a lack of data regarding nutrition adequacy among these patients, and although nitrogen balance has been studied as a marker of adequate protein intake in healthy individuals and acutely critically ill patients, it has not been well studied in critically ill patients with PMV. The purpose of this study was to determine if patients requiring PMV admitted to a long-term acute care hospital (LTACH) achieved registered dietitian (RD) recommended goals for energy and protein intake and if the recommendations were adequate to avoid negative nitrogen balance.

Methods: Using a retrospective, cohort study design, patients requiring PMV who had orders for 24-h urine collections for urea nitrogen (24hrUUN) were included. Energy and protein intake was calculated from chart documentation of dietary intake for the 24-h period during which patients underwent a 24hrUUN. Nitrogen intake was estimated from protein intake. Dietary intake was compared to RD-recommendations to determine the percentage of RD-recommendations achieved. Nitrogen balance was calculated as nitrogen intake minus nitrogen loss, with negative balance categorized as less than -1 . **Results:** Subjects ($n = 16$) were 38% male and 75% African American (mean age 61.5 ± 3.2 years; mean BMI 27.5 ± 2.5 kg/m²). Duration of LTACH hospitalization was 26.5 (6–221) days. Mean energy and protein intake was 21.7 ± 2.9 kcal/kg/d and 1.1 ± 0.1 g/kg/d, respectively, which corresponded to 86% of both RD energy and protein recommendations. Ten patients achieved a positive nitrogen balance (mean 0.9 ± 1.1 g). In addition, there was a positive linear relationship between protein intake and nitrogen balance ($r = 0.59$, $p = 0.016$).

Conclusion: Survivors of critical illness requiring PMV achieved a high percentage of RD-recommended protein and calories, and prevented a negative nitrogen balance in a majority of patients. Increasing protein intake can prevent a negative nitrogen balance. Future studies should evaluate whether these patients are able to maintain a steady state of nitrogen intake and excretion over time and how this affects time to and/or success of weaning.

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Abbreviations: PMV, Prolonged mechanical ventilation; LTACH, Long-term acute care hospital; RD, Registered Dietician; 24hrUUN, 24-h urine collections for urea nitrogen; BMI, Body mass index; NB, Nitrogen balance.

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1. Introduction

As a result of advances in medical care, more patients are surviving acute critical illness, with a high proportion of these patients requiring prolonged mechanical ventilation (PMV), defined as the need for ≥ 21 consecutive days of mechanical ventilation for ≥ 6 h/day [1]. Patients requiring PMV are at risk for multiple hospital readmissions, higher mortality, and poor quality of life post-discharge [2]. Additionally, they are at higher risk of malnutrition and complications, including nosocomial infections, impaired wound healing, and sarcopenia [3–5]. Specifically, for patients requiring PMV, malnutrition can lead to respiratory muscle fatigue and poor gas exchange, which can delay weaning from mechanical ventilation further prolonging hospital stay [6].

Both overfeeding and underfeeding have been associated with poor outcomes in critically ill patients [7–12], fueling the debate about the optimal nutritional intake in this population. Previous studies have demonstrated that varying levels of energy and protein delivery have yielded no difference in outcomes [13–15], while other data suggest that increasing protein intake to 1.2–1.5 g/kg/day may improve mortality in critically ill patients [5,6]. The majority of studies has focused on patients with acute critical illness, and has not assessed the nutritional requirements of survivors of critical illness requiring PMV treated in long-term acute care hospitals (LTACHs). Given the lack of data regarding these patients, it is unclear if survivors of critical illness requiring PMV are receiving adequate nutrition and whether this results in more favorable clinical outcomes, such as weaning from the ventilator. Typically, the energy and protein requirements of these patients are estimated from weight-based equations, which incorporate severity of illness, body mass index (BMI), and chronic medical problems [16]. Nitrogen balance has been used as a marker to assess adequate protein intake in healthy and acutely ill individuals but not chronically critically ill patients. Therefore, the purpose of this study was to determine if patients admitted to an LTACH requiring PMV achieved registered dietitian (RD)-recommended goals for energy and protein, and if these recommendations were adequate to avoid negative nitrogen balance.

2. Materials and methods

This retrospective cohort study examined mechanically ventilated patients at an urban, LTACH affiliated with the University of Maryland Medical Center from December 2015 to October 2016. The ventilator unit has 30 beds and a patient-nurse ratio of 6:1, a respiratory therapist-patient ratio of 9:1, 24-h hospitalist coverage, hemodialysis unit, and multidisciplinary support team consisting of physical, occupational, recreational, and speech therapists, and clinical pharmacist services, social worker, psychiatric liaisons, and nutritionists. Physical rehabilitation efforts consisted of passive range of motion exercises for ventilator-dependent patients. All patients had a tracheostomy and had ventilator settings requiring $\text{FiO}_2 \leq 60\%$ with $\text{SpO}_2 \geq 90\%$, PEEP ≤ 10 cm H₂O and were mechanically ventilated for at least 21 days during their hospital admission prior to transfer to our LTACH. The length of LTACH stay represented the number of days the patient was present in our LTACH, and excluded hospital days prior to LTACH admission, as there was limited access to the records of the patients preceding acute hospital stay. The patients in this study were dependent on nasogastric enteral feedings as the sole source of energy in order to meet their nutritional needs. This study received institutional review board exempt status.

Inclusion criterion was defined as survivors of critical illness receiving PMV in a LTACH who had a random 24-h urine collection for urea nitrogen (24hrUUN) performed for assessment of nitrogen

balance for failure to wean or wound healing. Medical records were reviewed to determine 24-h volume of enteral feeds administered during the 24-h period during which the 24hrUUN collection was completed. Energy (kcal) and protein (grams) intake were calculated based upon each patient's enteral feeding formula, including energy and protein from additional nutritional supplements, for the same 24-h period of urine collection. Nitrogen balance was calculated using total protein intake from enteral feeds and additional nutritional supplements to calculate nitrogen intake and the measured nitrogen excretion from the 24hrUUN by using the formula:

$$\text{Nitrogen balance} = (\text{grams protein intake} / 6.25) - (24\text{hrUUN} + 4) \quad (1)$$

where +4 represents nitrogen lost not in the form of urine urea (through sweat and GI losses).

Negative nitrogen balance was defined as nitrogen intake minus output less than -1 . The RD used the Penn State 2003b equation to calculate energy requirements adjusting for body temperature and minute ventilation. Dietary intake was compared to RD recommendations for energy and protein to determine the percent of RD recommendations achieved. Patients who received 80% of recommended energy and protein intake were considered to be at goal as suggested by the ASPEN and SCCM guidelines [17]. The results of 24-h urine specimens, which were collected to assess urine urea, were matched to corresponding 24-h protein intakes for estimation of nitrogen balance. Demographic data and total energy delivered were collected and calculated for the entire cohort, then stratified according to nitrogen balance status. All continuous data were expressed in mean \pm standard error of the mean (SEM) or median (interquartile range), and all categorical data were expressed as proportions. Linear regression was performed to determine the relationship between protein intake and nitrogen balance (SAS 9.4 Cary, NC, USA).

3. Results

The records of 17 patients were reviewed over a period of ten months. One patient was excluded due to an incomplete 24hrUUN collection. Patient demographics are presented in Table 1. The cohort was predominantly older with a mean age of 61.5 ± 3.2 years. Patients spent 56.5 (16–211) days on the ventilator and were in the LTACH for 26.5 (6–221) days. Primary ICU admission diagnoses were sepsis (44%; $n = 7$) and stroke (19%; $n = 3$) with the remaining diagnoses including pneumonia, heart failure exacerbation, post-operative care, acute pancreatitis, diabetic ketoacidosis, and subarachnoid hemorrhage.

Table 1
Baseline demographics of prolonged mechanically ventilated cohort.

Characteristic (n = 16)	Total
Age, years	61.5 \pm 3.2
Gender	
Male, n (%)	6 (38%)
Race, n (%)	
Caucasian	4 (25%)
African American	12 (75%)
Weight, kg	73.4 (44–133)
Body mass index, kg/m ²	27.5 \pm 2.5
Length of stay, days	26.5 (6–221)
Ventilator duration, days	56.5 (16–211) ^a

Data are presented as median \pm standard error of the mean, or median (interquartile range).

^a All patients were mechanically ventilated for at least 21 days including from outside hospital; data recorded from LTACH stay.

Patients received 21.7 ± 2.9 kcal/kg/day of the recommended goal of 25 kcal/kg/day and received 1.1 ± 0.1 g/kg/day in protein of the recommended goal of 1.2 g/kg/day. This corresponds to an achievement of 86% of RD energy and protein recommendations (Table 2). Eleven patients met $\geq 80\%$ of RD-recommended goal energy requirements, and 12 patients met $\geq 80\%$ recommended protein requirements. Mean nitrogen balance for all patients ($n = 16$) was 0.9 ± 1.1 (Table 3). Achieving recommended protein intake prevented a negative nitrogen balance in ten patients (mean -0.3 ± 0.9 g), while six were in negative balance during the 24-h period. Of the patients who received a net even or positive nitrogen balance, the mean nitrogen balance was 3.6 ± 0.1 . Of the patients who achieved a net negative nitrogen balance, the mean nitrogen balance was -3.6 ± 1.0 (Table 3). Sixty-two percent of patients (10/16) had a net positive nitrogen balance. A positive linear relationship existed between protein intake and balance, $r = 0.59$, $p = 0.016$ (Fig. 1).

4. Discussion

This study demonstrated that survivors of critical illness requiring PMV in an LTACH received a high percentage of RD-recommended energy and protein intake. Specifically: 1) Patients received on average 86% of their recommended energy and protein intake; 2) the majority of patients avoided a negative nitrogen balance; and 3) increasing protein intake trended towards an increase in nitrogen balance.

Multiple clinical assessments were used to determine nutritional status, including the measurement of serum protein markers such as albumin, transthyretin (prealbumin), and transferrin [18–20]. However, these markers are impacted by inflammation [21] and are poor indicators of nutritional status in critically ill patients. Given these limitations, nitrogen balance has been proposed to evaluate adequate nutritional intake. Nitrogen balance estimates total body protein from nitrogen intake and nitrogen excretion in the form of urine urea, and this relationship has been used to assess the adequacy of dietary protein intake in various patient populations. Negative nitrogen balance demonstrates a loss of nitrogen, signifying inadequate protein intake, and increasing nitrogen balance has shown a trend towards improved mortality in critically ill patients [22,23]. Although nitrogen balance has been investigated as a marker of adequate protein intake in healthy individuals and acutely critically ill patients, it has not been well studied in chronically critically ill patients requiring PMV.

Recent research has focused on identifying the optimal protein intake for critically ill patients [24,25], given that critical illness is associated with hypermetabolism and net protein catabolism [26].

Table 2
Caloric and protein intake achieved by the patient.

	Amount received	Amount rec	% RD rec achieved
Energy, kcal/kg/day	21.7 ± 2.9	25 ± 1.9	86%
Protein, g/kg/day	1.1 ± 0.1	1.2 ± 0.1	86%

All data expressed as mean \pm standard error of the mean. Rec = recommended.

Table 3
Mean nitrogen balance.

	Nitrogen balance
All patients ($n = 16$)	0.9 ± 1.1
Patients achieved net even or positive NB	3.6 ± 0.1
Patients achieved net negative NB	-3.6 ± 1.0

All data expressed as mean \pm standard error of the mean. NB = nitrogen balance.

The chronically ill state of inflammation experienced by our LTACH cohort [27] likely requires greater amounts of protein to support the immune system. Increasing protein intake to $\geq 80\%$ of goal protein intake has been associated with reduced mortality [28]. Increasing protein intake decreases protein breakdown and increases protein synthesis, which increases nitrogen balance. This is evidenced by Dickerson's work in critically ill patients, which demonstrated minimal changes in nitrogen balance at protein intake < 1.5 g/kg/day and a modest improvement in nitrogen balance with protein intake between 1.5 and 2 g/kg/day [29]. In a study of moderately malnourished elderly patients, increased protein intake also led to increased lean body mass [30]. Preservation of muscle mass is important to prevent loss of muscle function. Although a lack of large randomized trials have examined the relationship between nitrogen balance and protein intake on clinical outcomes for critically ill patients [31], increasing nutritional adherence and protein intake in this population may prevent negative nitrogen balance and may favorably decrease the loss of muscle mass. It is important to consider that enteral feeds are standardized, and increasing protein solely using enteral feed will also increase total energy. Patients may benefit more from protein supplements to increase protein while maintaining energy intake to avoid overfeeding.

The ASPEN clinical guidelines focus on critically ill patients with an expected length of stay greater than 2 or 3 days. Few studies have been conducted in critically ill patients who require a length of stay > 3 weeks, as experienced by our cohort [1,32]. Further research studying optimal energy and protein requirements in this population to ensure clinical rehabilitation is complemented by optimum nutrition for patients in the LTACH setting is necessary.

To our knowledge, this is the first study that has investigated nutritional intake and its relationship to nitrogen balance in chronically critically ill patients in an LTACH requiring PMV. Our study has several limitations. First, this study's size, single-center and retrospective observational nature, and the collection of data including tube feedings relied on nursing and RD chart documentation, which is susceptible to inaccuracies due to inconsistent or lack of documentation of received feedings or interruptions to enteral feeding [33]. Another study limitation is determining the accuracy of the nitrogen balance equation in chronically critically ill patients. The equation of nitrogen balance is defined as nitrogen intake minus nitrogen excretion, which is measured by $24\text{hrUUN} + 4$. The addition of 4 to urine urea nitrogen estimates all non-urine urea nitrogen losses (e.g., losses through the skin, sweat, and gastrointestinal losses). It is unclear in this patient population how much nitrogen is excreted in non-urine urea forms, and if a total of four is enough to encompass those losses. Normal daily variability in nitrogen excretion occurs in healthy populations, which is further complicated by the potential for abnormal gastrointestinal losses via diarrhea, blood loss via wounds or hemorrhage, sputum loss, and loss through skin during fever that may be experienced by the critically ill population. In our study, we were limited to examining one 24-h time period; thus, future studies should attempt to capture these other sources of nitrogen loss over a longer period of time.

Nitrogen balance measures protein intake and excretion, but not necessarily the rate of protein synthesis or protein catabolism. Initial studies evaluating nitrogen balance equation were done in healthy individuals [34–36]. Critically ill patients tend to undergo a higher rate of protein breakdown, which further contributes to the progression of their disease and morbidity and mortality [19]. Stress, including emotional and environmental stress, may also negatively influence nitrogen balance and influence protein metabolism [37]. Physical trauma, sleep disruption, and illness, as experienced by critically ill patients, negatively impact body protein status and nitrogen balance [37]. Despite existing recommendations

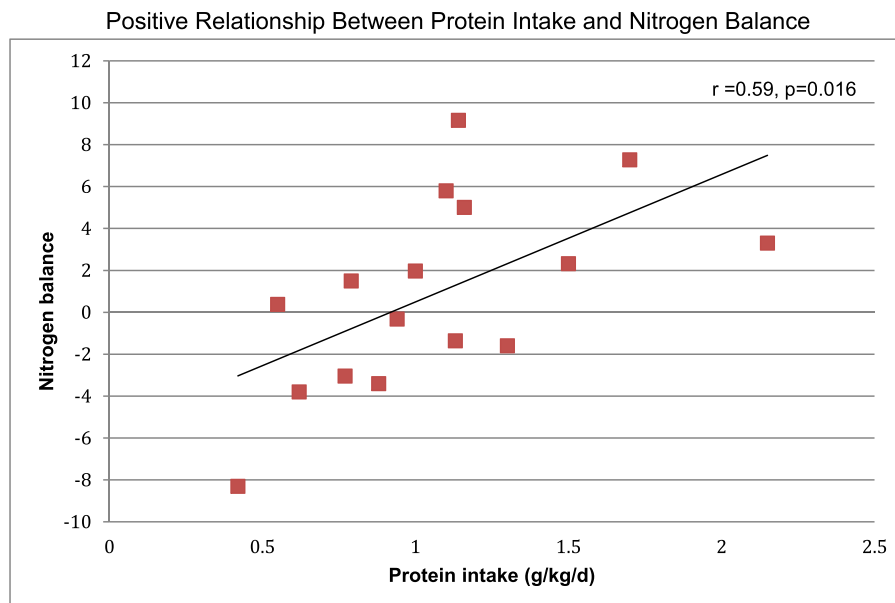


Fig. 1. Scatterplot graphing protein intake against nitrogen balance demonstrating a positive linear relationship between nitrogen intake and balance.

to compensate for these nitrogen losses by increasing protein intake, chronically critically ill patients in LTACHs have frequent interruptions in their feedings due to high gastric residuals and vomiting, leading to fluctuations in protein intake. Given this, it is unclear if the patients in this study achieved steady state of nitrogen metabolism. Although our study demonstrated that 62% of patients avoided a negative nitrogen balance, considering the limitations discussed above, it cannot be assumed that RD-recommendations will prevent a negative nitrogen balance.

5. Conclusion

Survivors of critical illness requiring PMV in an LTACH received a high percentage of the RD-recommended protein and energy intake, which resulted in a majority of patients avoiding a negative nitrogen balance. Future studies should investigate if these high nutritional-risk patients continue to avoid a negative nitrogen balance during their hospitalization after achieving a steady state of nitrogen intake and excretion and whether achieving and sustaining positive nitrogen balance impacts clinical outcomes, such as time to weaning from mechanical ventilation and overall weaning success. In addition, studies should incorporate 3-methyl histidine or other markers of muscle protein turnover to more accurately assess the associations of protein intake, nitrogen balance equilibrium and changes in muscle mass.

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Authors' contributions

SB and ACV have full access to the data and take full responsibility for the integrity and the accuracy of the data. SB, ACV, MS, EAP, MDA, JD, MTM collected the data. SB, DHT, ACV analyzed the data. SB, DHT, ACV prepared and reviewed the manuscript. ACV supervised the research. SB, ACV designed the study. All authors have provided critical revision for important intellectual content and have read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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