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JPEN J Parenter Enteral Nutr 2012 36: 60 originally published online 13 December 2011
DOI: 10.1177/0148607111415109

2011 Premier Research Paper

Journal of Parenteral and Enteral Nutrition
Volume 36 Number 1
January 2012 60-68

10.1177/0148607111415109
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Optimal Protein and Energy Nutrition Decreases Mortality in Mechanically Ventilated, Critically Ill Patients: A Prospective Observational Cohort Study

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Financial disclosure: none declared.

Background: Optimal nutrition for patients in the intensive care unit has been proposed to be the provision of energy as determined by indirect calorimetry and the provision of protein of at least 1.2 g/kg. *Methods:* Prospective observational cohort study in a mixed medical-surgical intensive care unit in an academic hospital. In total, 886 consecutive mechanically ventilated patients were included. Nutrition was guided by indirect calorimetry and protein provision of at least 1.2 g/kg. Cumulative intakes were calculated for the period of mechanical ventilation. Cox regression was used to analyze the effect of protein + energy target achieved or energy target achieved versus neither target achieved on 28-day mortality, with adjustments for sex, age, body mass index, Acute Physiology and Chronic Health Evaluation II, diagnosis, and hyperglycemic index. *Results:* Patients' mean age was 63 ± 16 years; body mass index, 26 ± 6; and Acute Physiology and Chronic Health Evaluation II, 23 ± 8. For neither target, energy target, and protein + energy target, energy intake was 75% ± 15%, 96% ± 5%, and 99% ± 5% of target, and protein intake was 72% ± 20%, 89% ± 10%, and 112% ± 12% of target, respectively. Hazard ratios (95% confidence interval) for energy target and protein + energy target were 0.83 (0.67–1.01) and 0.47 (0.31–0.73) for 28-day mortality. *Conclusions:* Optimal nutritional therapy in mechanically ventilated, critically ill patients, defined as protein and energy targets reached, is associated with a decrease in 28-day mortality by 50%, whereas only reaching energy targets is not associated with a reduction in mortality. (*JPEN J Parenter Enteral Nutr.* 2012;36:60-68)

Keywords: critical care; calorimetry; outcomes research; protein and energy goal-oriented therapy; protein requirements

Clinical Relevancy Statement

In clinical practice, the critically ill patient frequently is not fed adequately for a number of reasons. However, to make a step forward, we have to (1) identify individual targets of energy and protein intake (optimal nutrition), (2) manage to achieve these targets, and (3) show that reaching targets is relevant to outcome. We found that mortality can be reduced substantially by optimal nutrition. These prospective observational findings may contribute to the awareness of intensive care unit (ICU) physicians that nutrition is in fact a relevant matter in treating the ICU patient. Further randomized controlled trials are needed. We know that achieving nutrition targets will not always be possible, but we believe that optimal nutrition is feasible and clinically relevant.

Introduction

Optimal nutrition therapy aims at conservation or restoration of the body protein mass and provision of adequate amounts of energy. One proposed definition of optimal

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Received for publication January 10, 2011; accepted for publication March 31, 2011.

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nutrition is provision of energy meeting energy expenditure as assessed by indirect calorimetry, as well as protein provision of more than 1.2 g/kg of preadmission weight for critically ill patients.[1] Actual measurement of energy expenditure, as preferred over predicted energy expenditure, has been incorporated in the recent ESPEN guidelines for intensive care.[2] The evidence base for protein requirements of critically ill patients is still limited, but there are some convincing studies to support the prescription of at least 1.2 g/kg.[3–5]

Inadequate provision of energy correlates with the occurrence of complications, such as acute respiratory distress syndrome, infections, renal failure, pressure sores and need for surgery, and mortality.[6–9] Recent results of a prospective randomized controlled pilot study show that tight control of energy balance through provision of energy guided by indirect calorimetry by enteral and parenteral nutrition led to cumulative positive energy balances, whereas the control group (targeted at 25 kcal/kg) had negative cumulative energy balances. More important, hospital mortality decreased in the intervention group, but at the same time, length of hospital stay and complication rate increased.[10]

Larger studies, aimed to improve nutrition support by implementing evidence-based algorithms, have failed to demonstrate significant beneficial effects on survival, but the nutrition targets described above were never achieved.[11–13] These studies therefore cannot be used as evidence against the concept that nutrition is relevant for outcome in critically ill patients.

We recently developed a nutrition algorithm to improve nutrition therapy (see Figure 1). Our nutrition algorithm,[14] fully incorporated into our patient data management system,[15] selects an appropriate nutrition formula for a patient and provides adequate pump speed to reach prespecified optimal protein and energy targets as described above. In a previous, smaller, and therefore possibly insufficiently powered study, we were able to show beneficial effects on mortality, however in females only.[16]

In the current, larger, prospective observational study—based on a cohort of 886 mechanically ventilated, critically ill patients undergoing indirect calorimetry—we aimed to investigate the effects of our nutrition-targeted approach on clinical outcome.

Materials and Methods

This is a prospective observational study in mixed medical-surgical patients in a tertiary university hospital. According to the American Association of Respiratory Care guideline,[17] we focused on patients who require long-term intensive care. These critically ill patients were included if on day 3–5 (timing of indirect calorimetry), the predicted period of need for artificial nutrition was at least 5–7 additional days, as admitted to ICU between August 2004 and March 2010. Other inclusion criteria were indirect calorimetry measurement performed, age over 18 years, and first admission to the ICU with indirect calorimetry measurement. Exclusion criteria were $FiO_2 > 0.6$, air leaks through cuffs and/or chest drains, and unavailable metabolic monitor and/or personnel.

The study was approved by the ethics committee of the VU University Medical Center. Informed consent was waived because the study protocol included only variables that are routinely performed in clinical practice.

Early enteral feeding is initiated in hemodynamically stable patients within the first 24 hours of admission to the ICU (see Figure 1). The route of administration is preferably via the gastrointestinal tract. We allow gastric residuals up to 250 mL per 6 hours. If residuals surpass this amount, we administer erythromycin (1–3 mg/kg body weight) for 2 days and continue feedings. In case of limited effect of this medication, postpyloric feeds are administered. Parenteral nutrition is provided only when the gut fails (fistulas, short bowel, obstruction); it is not given as parenteral supplementation to inadequate amounts of enteral nutrition in the early phase of nutrition therapy.

When enteral nutrition is initiated, energy requirements are predicted by Harris Benedict[17,18] with added 20% for stress[19] and 10% for activity,[20] until indirect calorimetry is performed. Indirect calorimetric measurements are performed as part of routine care, usually between days 3–5 after admission.[17] Indirect calorimetry was performed with a Deltatrac MBM-100 Metabolic Monitor (Datex-Engstrom Division, Instrumentation Corp, Helsinki, Finland) connected to the mechanical ventilator. After calibration of the device, measurements were performed over a period of 1.0–1.5 hours in resting steady-state conditions with a maximum coefficient of variation of 10%. Thereafter, the energy target was equivalent to resting energy expenditure by indirect calorimetry with 10% added for activity, and nutrition was adjusted accordingly within 24 hours to meet the new energy target. Repeated measurements were performed when clinically indicated.[17] Protein was provided with a target of 1.2–1.5 g/kg of preadmission body weight, according to national guidelines on protein provision; for patients with body mass index (BMI) > 30, body weight was adjusted (based on BMI of 27.5 kg/m^2) with corresponding protein requirement.[21] To achieve energy and protein targets, we used an algorithm for enteral nutrition that determines the nutrition formula (product) and amount to be given to meet both requirements in a patient.[14] The enteral nutrition formulas used were as follows: Nutrison Standard (total energy, 1,000 kcal/L; protein, 40 g/L) and Nutrison Protein Plus (1,250 kcal/L and 63 g/L), both from Numico, Zoetermeer, Netherlands, and Promote (1000

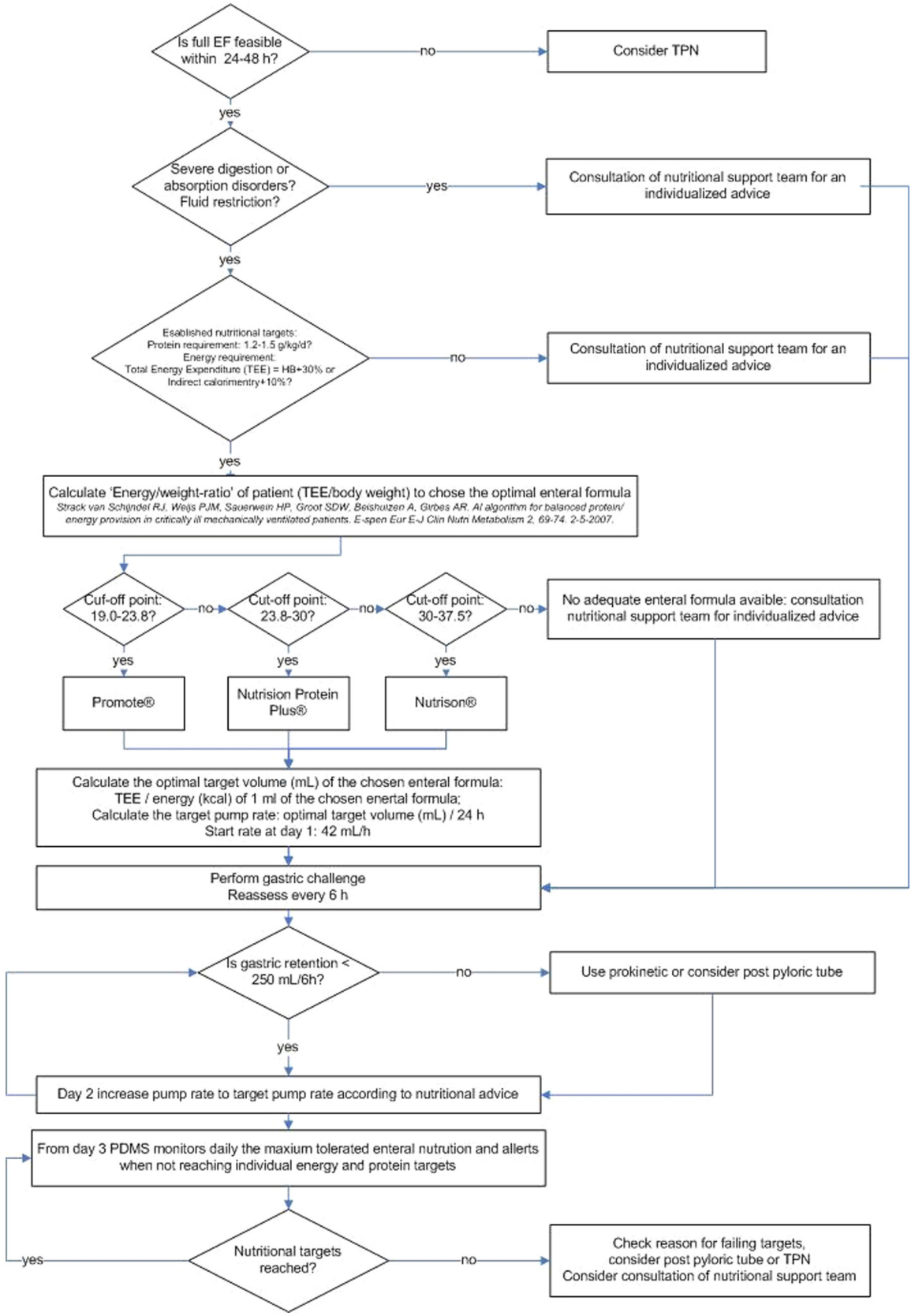

Figure 1. Nutrition policy at the intensive care unit at the VU University Medical Center.

kcal/L and 63 g/L), from Abbott Nutrition, Hoofddorp, Netherlands. Parenteral nutrition during the study period was initially provided by our pharmacy as an all-in-one admixture containing 1,000 kcal/L and 47 g/L of amino acids; later, a commercially available product was used (Struktokabiven, Fresenius-Kabi, Bad Homburg, Germany) containing 1,050 kcal/L and 50 g/L of amino acids.

Data from indirect calorimetric measurements were entered in our data management system (Metavision, IMD-Soft, Israel).

For every patient, the following were recorded: age, sex, weight and height, BMI, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, diagnosis group, length of ventilation, length of stay in the ICU, measured energy expenditure, daily energy and protein intake from all sources during the period of mechanical ventilation, and all blood glucose values during the ICU admission period. For every patient, the probability of death was calculated from the APACHE II score, from which the standardized mortality ratio for groups was calculated.[22]

For weight and height of the patients, we used preadmission data retrieved from the preassessment outpatient clinic, from earlier measurements done during admission, or from data obtained in other healthcare settings. Otherwise, the relatives or, if possible, the patient was asked to provide these data. If these data could not be retrieved, weight and height were estimated by 2 experienced intensivists and the mean value used; supine height was measured by experienced intensivists.

Cumulative energy and protein intakes were calculated for the entire period of mechanical ventilation. Patients were categorized into 4 groups according to whether energy and protein targets were reached or not reached: neither protein nor energy target reached (NT), both protein and energy target reached (PET), only energy target reached (ET), only protein target reached (PT).

Determining the adequacy of the glycemic control was performed by calculation of the hyperglycemic index in mmol/L per patient during the entire ICU period. The average number of glucose samples per patient was 6.2 per day. The hyperglycemic index is defined as the area under the concentration-time curve above the upper limit of normal (glucose level, 6.0 mmol/L) divided by the total length of ICU stay.[23]

Statistical Analysis

Descriptive data are reported as mean ± SD and/or median (interquartile range) for skewed distributions or as frequency and percentage. Kruskal-Wallis and analysis of variance with post hoc Bonferroni were used to compare target groups. Cox regression analysis was used with length of hospital stay as the time variable; with ICU, 28-day, and hospital mortality as outcome variable; and with PET achieved (yes/no) or ET achieved (yes/no) as independent variable. Hazard ratios (HRs; 95% confidence interval) were adjusted for sex, age, BMI, APACHE II score, diagnosis category, and hyperglycemic index. SPSS 17 (SPSS Inc, Chicago, IL) was used for statistical analysis. A second model was generated to assess the possible confounding effect of the time to reach the energy target (in days) and the amount of parenteral nutrition (in mL/d, based on the whole period of mechanical ventilation). $P < .05$ was considered statistically significant.

Results

A total of 886 sequential patients fulfilled the inclusion criteria: 647 patients (73%) were fed exclusively with enteral nutrition; 9 (1%) were exclusively fed with parenteral nutrition; and 230 (26%) received enteral and parenteral nutrition during the period of mechanical ventilation.

Table 1 shows patient characteristics, nutrition intake, and outcome data categorized by target group. The group of patients that reached only the protein target but not the energy target was not further considered statistically, because of the small number of patients in this group (n = 24). For the NT, ET, and PET groups, energy intake was 75% ± 15%, 96% ± 5%, and 99% ± 5% of target, and protein intake was 72% ± 20%, 89% ± 10%, and 112% ± 12% of target, respectively. Table 2 illustrates results related to nutrition intake and variables related to patient outcomes (number of ventilator days, length of ICU stay, length of hospital stay). Length of ICU and total hospital stay (days) and number of ventilator days were shorter in the NT group compared to the ET and PET groups ($P < .05$). ICU, 28-day, and hospital mortality were not significantly different across target groups ($P > .05$).

Table 3 shows HRs for ICU, 28-day, and hospital mortality for model 0 (unadjusted HR), model 1 (adjusted for sex, age, BMI, APACHE II score, diagnosis category, and hyperglycemic index), and model 2 (additionally adjusted for time to reach energy target in days and amount of parenteral nutrition used). Figure 2 shows that adjusted HRs did not change or only slightly improved 28-day mortality. Post hoc subgroup analysis per diagnosis revealed that patients with sepsis showed increased HR. Effect modification by sex was not found (as was observed in Strack van Schijndel et al[16]).

Discussion

Setting and reaching personalized energy and protein targets in mechanically ventilated, critically ill patients results in a 50% decrease of 28-day hospital mortality compared to those patients that do not reach either target. Meeting only the energy target appears to be insufficient for improvement of outcome and thus for optimal nutrition. This observation underscores the importance of dietary protein intake, especially in critically ill patients who depend on artificial nutrition for a relatively long period.

Table 1. Patient Characteristics[a]

	No Target	Protein + Energy Target	Energy Target	Protein Target	All
No. of patients	412	245	205	24	886
Age, y	62.6 ± 16.0	62.7 ± 15.7	63.8 ± 16.6	55.6 ± 19.5	62.7 ± 16.2
Men, %	72.1	53.1	55.1	79.2	63.1[b]
Admission diagnosis, %[c]					
No. of patients	399	238	198	24	859
Trauma	5.3	6.7	4.5	12.5	5.7
Sepsis	11.5	17.2	16.7	20.8	14.6
Respiratory	17.0	22.7	26.3	16.7	20.7
Surgical	24.1	26.5	22.7	16.7	24.2
Neurologic	7.0	7.6	10.6	4.2	7.9
Postreanimation	13.5	2.5	5.6	0.0	8.3
Metabolic/renal	1.0	1.7	2.0	4.2	1.5
Cardiovascular	17.5	12.2	9.6	20.8	14.3
Other	3.0	2.9	2.0	4.2	2.8
Body weight, kg	82 ± 18	69 ± 17[d]	75 ± 16[d,e]	76 ± 26	77 ± 18[f]
Body height, cm	174 ± 9	170 ± 10[d]	171 ± 10[d]	173 ± 10	172 ± 10[f]
Body mass index, kg/m^2	27 ± 6	24 ± 6[d]	25 ± 5[e]	25 ± 8	26 ± 6[f]
Acute Physiology and Chronic Health Evaluation II					
Mean ± SD	23 ± 8	23 ± 8	23 ± 8	22 ± 9	23 ± 8
No.	399	238	198	24	859
Hyperglycemic index					
Mean ± SD	1.32 ± 0.57	1.11 ± 0.45[d]	1.19 ± 0.51[d]	1.03 ± 0.55	1.22 ± 0.53[f]
No.	408	245	203	24	880

[a]Values as mean ± SD.
[b]Kruskal-Wallis test indicated significantly different proportion of men across groups.
[c]In percentages except for No. of patients.
[d]Analysis of variance with post hoc Bonferroni indicated significant difference from no-target group.
[e]Analysis of variance with post hoc Bonferroni indicated significant difference from Protein + Energy target group.
[f]One-way analysis of variance indicated significant target group effect.

There are several challenges in defining and attaining optimal nutrition as well as observing an outcome benefit.

First, optimal nutrition needs to be defined. A recent definition of optimal nutrition has been proposed, as (1) energy supply according to measured energy expenditure by indirect calorimetry plus 10% for activity and (2) protein supply of at least 1.2 g/kg of preadmission weight for mechanically ventilated, critically ill patients.[1] The *Guideline Perioperative Nutrition* of the Dutch Institute for Healthcare Improvement adopted these recommendations, although with estimated rather than measured energy expenditure by indirect calorimetry.[21] The National Healthcare Inspectorate indicator for adequate nutrition therapy of malnourished patients uses protein intake of at least 1.2 g/kg/d on day 4 from admission. Evaluation of effectiveness of the present definition of optimal nutrition is therefore of academic and practical importance.

The second challenge is to achieve optimal nutrition. First, we had to acknowledge that setting targets for energy and protein, which are derived from different concepts, would change the demands on the nutrition formula of enteral and parenteral feeding. A standard formula and a 2-L/d bag policy would not result in optimal nutrition. We performed a theoretical evaluation of our patient population and found that only about 25% of patients would reach their energy and protein target with 1 standard formula. Therefore, we developed an algorithm that is easily applied to individual patients, requiring only body weight and energy needs.[14] The algorithm subsequently recommends an enteral formula and pump speed based on the limits for an optimal protein supply of 1.2–1.5 g/kg. This approach theoretically results in about 90% of patients reaching their energy and protein targets. In real practice, the percentage of our patients reaching their protein target increased from 30% to about 60% after introduction of the algorithm into our patient data management system.[15]

The third challenge is to prove that it is of clinical benefit to the patient when optimal nutrition is set by targets and these targets are reached. We present the first prospective study to investigate outcome effects of achieving energy and protein targets. It is quite remarkable that when we consider the NT group, which had a mean protein intake of

Table 2. Nutrition Therapy and Clinical Outcome[a]

	No Target	Protein + Energy Target	Energy Target	Protein Target	All
No. of patients	412	245	205	24	886
Energy					
Intake, kcal/d	1572 ± 404	1897 ± 359[b]	1819 ± 333[b]	1898 ± 384	1728 ± 403[c]
Target, %	74 ± 15	99 ± 9[b]	96 ± 5[b,d]	85 ± 4	86 ± 16[c]
Protein intake					
g/d	67 ± 21	89 ± 15[b]	78 ± 15[b,d]	88 ± 19	76 ± 20[c]
g/kg/d	0.83 ± 0.23	1.31 ± 0.18[b]	1.06 ± 0.14[b,d]	1.21 ± 0.15	1.02 ± 0.28[c]
Parenteral nutrition					
% of patients	18.2	38.4	29.8	37.5	27.0[e]
mL/d	108 ± 310	297 ± 537	131 ± 301	396 ± 604	173 ± 403
Intake d1–3					
Energy, kcal/d	808 ± 379	1266 ± 545[b]	1094 ± 436[b,d]	876 ± 433	1003 ± 486
Protein, g/d	22 ± 19	47 ± 28[b]	34 ± 21[b,d]	28 ± 23	32 ± 24
Time to target, d					
Energy	3.5 ± 5.1	1.7 ± 1.5[b]	2.1 ± 2.0[b]	2.5 ± 2.3	2.7 ± 3.8[c]
Protein	3.6 ± 5.4	3.3 ± 5.0	3.9 ± 5.8	3.1 ± 4.1	3.6 ± 5.4
Length of ventilation, d					
Mean ± SD	16.4 ± 16.6	28.3 ± 17.0[b]	25.4 ± 17.9[b]	27.1 ± 24.3	22.1 ± 18.0[c]
Median (interquartile range)	12 (11)	25 (20)	20 (21)	20 (23)	17 (18)
Length of intensive care unit stay, d					
Mean ± SD	18.8 ± 18.0	31.7 ± 19.6[b]	28.0 ± 18.3[b]	28.8 ± 24.5	24.8 ± 19.5[c]
Median (interquartile range)	14 (13)	26 (22)	22 (24)	21 (22)	19 (19)
Length of hospital stay, d					
Mean ± SD	40.1 ± 35.0	65.7 ± 58.4[b]	49.9 ± 38.9[b,d]	59.1 ± 56.6	49.9 ± 45.4[c]
Median (interquartile range)	31 (36)	53 (51)	42 (40)	44 (34)	39 (40)
Mortality, %					
Intensive care unit	17.7	22.4	23.9	16.7	20.4
28 d	20.4	14.7	19.5	12.5	18.4
Hospital	31.3	39.5	36.6	20.8	34.4

[a]Missing values are indicated with exact number of observations for the specific variable. Values as mean ± SD.
[b]Analysis of variance with post hoc Bonferroni indicated significant difference from no-target group.
[c]One-way analysis of variance indicated significant target group effect.
[d]Analysis of variance with post hoc Bonferroni indicated significant difference from Protein + Energy target group.
[e]Kruskal-Wallis test indicated significantly different portion with parenteral nutrition across groups.

Table 3. Relationship Between Nutrition Therapy and Intensive Care Unit, 28-Day, and Hospital Mortality[a]

	Protein and Energy Target	Energy Target
Model 0[b]		
Intensive care unit	0.91 (0.64–1.31), $P = .626$	1.03 (0.86–1.25), $P = .733$
28 d	**0.59 (0.40–0.88), $P = .010$**	0.90 (0.74–1.09), $P = .291$
Hospital	**0.76 (0.58–0.99), $P = .041$**	0.93 (0.81–1.08), $P = .339$
Model 1[c]		
Intensive care unit	0.79 (0.54–1.17), $P = .242$	0.99 (0.81–1.20), $P = .886$
28 d	**0.51 (0.33–0.78), $P = .002$**	0.84 (0.68–1.03), $P = .085$
Hospital	**0.70 (0.53–0.94), $P = .017$**	0.91 (0.79–1.06), $P = .233$
Model 2[d]		
Intensive care unit	0.72 (0.48–1.09), $P = .116$	0.98 (0.80–1.19), $P = .834$
28 d	**0.40 (0.26–0.64), $P < .001$**	**0.79 (0.64–0.97), $P = .024$**
Hospital	**0.62 (0.46–0.84), $P = .002$**	0.89 (0.77–1.04), $P = .137$

[a]Presented as hazard ratio (95% confidence interval). Bold font indicates significance ($P < .05$).
[b]Unadjusted.
[c]Adjusted for sex, age, body mass index, diagnosis, hyperglycemic index, and Acute Physiology and Chronic Health Evaluation II score.
[d]Additionally adjusted for time to energy target and use of parenteral nutrition.

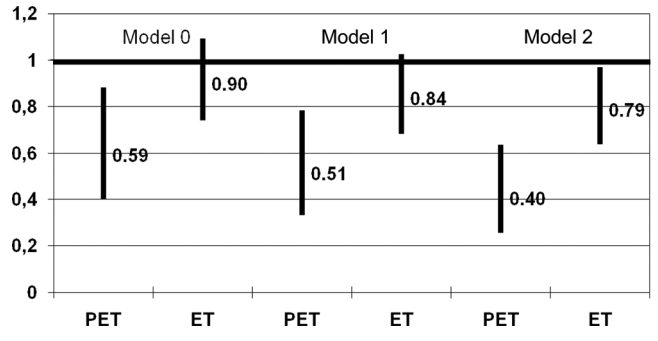

Figure 2. The 28-day mortality hazard ratio with 95% confidence interval for protein and energy target (PET) group and energy target (ET) group. Model 0 is unadjusted. Model 1 adjusted for sex, age, body mass index, diagnosis, hyperglycemic index, and Acute Physiology and Chronic Health Evaluation II score. Model 2 additionally adjusted for time to energy target and use of parenteral nutrition.

more than 0.8 g/kg, we still observe an impressive improvement in outcome in the groups in whom energy targets and especially the protein targets are actually achieved. Achievement of only energy targets does not appear to be sufficient, although our NT group already had a mean energy intake of almost 1,600 kcal/d, which is already much higher than that in other outcome studies.[11–13] Moreover, these previous studies implementing nutrition guidelines have not resulted in noticeable improvements in protein and energy nutrition as well as outcome[11–13] and are difficult to compare to our study. Mean reported protein intake < 0.5 g/kg[12,13] appears to be much lower even than 0.8 g/kg in our NT group or 1.3 g/kg in our PET group. The present study clearly shows that reaching preset nutrition targets is feasible in a dedicated center with a focus on clinical nutrition. Although data were included from 2004, reaching nutrition targets was most successful almost a year after introduction of the computer-assisted nutrition algorithm in 2006,[15] which is probably related to necessary changes in attitudes and behavior of staff (nurses) in using the algorithm within our patient data management system to its full potential. Over the whole observation period, the data from this study show that only 1 in 4 patients reached both nutrition targets, while we were able to increase this to almost 2 out of 3 patients by early 2008. There was no selection in patients, other than that it was mandatory that indirect calorimetry be performed early during ICU stay.

The international multicenter observational study by Alberda et al[24] already reported significant effects of energy and protein supply, studying a total of 2,772 mechanically ventilated ICU patients. However, their reported intakes are much lower than ours: only a mean 59% of energy and 56% of protein, compared to 86% for both energy and protein in the total group. One should take into account that their intake is derived from only the first 12 days of observation, while our data are based on the entire length of ventilation: The median length of ventilation is 9.0 days for the Alberda study and 22.1 days in the present study. Alberda et al argued that with more nutrition days, it is more likely to cover the initial energy deficit. This is actually part of the important message that reaching the targets matters and that not only should the first days or first week be considered but the whole period of nutrition therapy. For this reason we present mortality risk data for patients that reach the preset targets or not, instead of presenting mortality risk for an arbitrary increase of 1,000 kcal or 30 g of protein, as in the Alberda study. The arguable downside is that we chose an arbitrary cutoff point (target), but we provide our arguments for these targets above. The Alberda study[24] nicely shows that nutrition therapy is relevant not only to the malnourished group with BMI < 20 but also for so-called normal weight patients (BMI, 20–25) and obese patients (BMI > 35).

The prospective randomized controlled Tight Calorie Control Study (n = 112) recently showed that energy and protein intakes, averaged over the first 14 days of ICU admission, improved significantly in the tight calorie control group versus the control group (1,976 vs 1,838 kcal/d; protein, 76 vs 53 g/d).[10] The percentage of energy target actually delivered to patients in that study and control group corresponds exactly to our ET and NT groups (96% and 73%), and the percentage of protein target (79% and 57%) is highly comparable to our study. Major outcomes are a lower hospital mortality but also increased length of stay and increased infectious complications. A major difference is that parenteral nutrition has been used to obtain an energy supply that meets the target; therefore, comparison is hampered, but overall this randomized study confirms our observational findings.

Higher body weight appears to be important, as administration of the volume of enteral nutrition formulas is a limiting factor early in the course of nutrition therapy; therefore, patients with smaller body weight are more likely to reach their nutrition targets. When patients are split into groups with body weight higher and lower than the median value of 75 kg, the effect of PET or ET is the same for heavier and lighter patients (data not shown). Since most women in our study are under 75 kg, the lower body weight could have been of influence on the effect modification by sex as previously reported by our group.[16] However, any discussion on the causative effect remains speculative, as this is an observational study and not a randomized controlled trial.

By using prespecified targets and categorizing patients into target groups, we gained insight into the important contribution of protein as well as energy supply. Alberda et al argued that there is a fixed ratio between energy and protein.[24] However, by introducing our nutrition algorithm into computer-assisted nutrition therapy, we have been able to use different feeding formulas specifically aimed at reaching nutrition targets.[14,15] In this context, the protein target is based on body weight, and the energy target is based on measured energy expenditure. Also, measured

energy expenditure can be different (lower and higher) from predicted energy expenditure based on body weight, and this appears to be worse in patients compared to healthier groups.[25–27] Thus, protein needs are by definition fixed to body weight, but energy expenditure is more variable relative to fixed body weight. By using different enteral formulas, we increased protein intake (g/kg) by 58% (PET vs NT). This appears to be a unique feature of our study and provides an opportunity to compare energy plus protein vs energy alone, which cannot be accomplished by applying a fixed enteral formula. Another difference between PET and ET is that protein is derived from only nutrition formula, while energy can be derived from glucose infusion and fat-containing medication (eg, propofol). There are also endogenous sources of energy available, while lean body protein mass is heavily compromised during critical illness.[28] The importance of protein targets for optimal nutrition therapy has been stressed before.[16,28] The protein target group appears to perform well, but the small number of patients (n = 24) restricts conclusions. Therefore, especially in the long-stay, mechanically ventilated, critically ill patient, protein and energy targets should both be considered for optimal nutrition.

The energy deficit occurs especially in the first days after admission, when targeted volume cannot be administered for practical reasons such as gastric retention, slow increase of nutrition volume toward the targeted volume, hemodynamic instability, and diagnostic and therapeutic interventions.

Preliminary results show that provision of > 1,500 kcal/d in the first 3 days of admission, excluding parenteral glucose, reduces ICU and hospital mortality,[29] and more evidence accumulates about the relevance of early feeding.[30] Early provision of energy diminishes the cumulative caloric deficit. The current focus on early nutrition therapy—most likely with enteral nutrition supplemented with parenteral nutrition—may be beneficial for critically ill patients.[31,32] However, those patients with a long stay (mean duration of mechanical ventilation in this study is > 3 weeks) clearly require a protein-energy goal-oriented therapy.[33] Although our nutrition policy is to start enteral nutrition as early as possible, we have to state explicitly that our nutrition policy does not include supplementing inadequate enteral nutrition with parenteral nutrition. Nonetheless, it appears from the results of our study that addition of parenteral feeding does indeed contribute to reaching targets (as shown in Table 2). However, when HRs in the current study were adjusted for time to reach energy target as well as for the amount of parenteral nutrition used, there was no change or rather a slight improvement in the effect of achieving nutrition targets or not on 28-day mortality. This indicates that the effect of energy and protein targets reached cumulatively over the whole period of mechanical ventilation appears to be independent from early nutrition or the use of parenteral nutrition.

The main limitation of our study is the observational nature of the design. Randomized trials are needed for actual cause-effect relationships to be substantiated. In the present analysis we adjusted HRs for sex, age, BMI, APACHE II, diagnosis group, and glycemic control; however, other factors might be relevant for outcome as well. Another limitation is that setting protein and energy targets as we did is not as evidence based as we would like them to be, because of lack of adequate studies on protein and energy requirements of mechanically ventilated, critically ill patients.[3–5,34] Another point is that patients' nutrition intake is evaluated over the period of mechanical ventilation and not over the entire hospital stay. After weaning from mechanical ventilator and when oral feeding is an option, it is much more difficult to monitor all nutrition intake of the patient. We can assume—and, in fact, we have evidence—that nutrition intake on the nursing wards is less optimal. This may relate to a relatively high hospital mortality in the PET group, although this group had more patients with sepsis and patients who required parenteral nutrition. The main strength of this study is the large sample size from a single center. Another strength is that we have a consistent nutrition policy fully automated and computer guided by implementation of a nutrition algorithm that automatically selects the appropriate enteral nutrition[14] or parenteral nutrition[35] formula needed for a patient to reach energy and protein targets, along with the correct pump speed. Another strength is that all patients had their individual energy needs measured by indirect calorimetry.

Conclusion

Our study shows that successfully reaching a predefined energy target and protein target cumulative over the whole period of mechanical ventilation—with energy provision guided by indirect calorimetry and with protein provision guided by at least 1.2 g/kg of preadmission body weight—is associated with a decrease in 28-day mortality as much as 50%. Reaching only the energy targets does not appear to be sufficient, although it should be kept in mind that our control group (NT) already had a mean energy intake of almost 1,600 kcal/d. We are in need of randomized controlled trials to show the real value of protein and energy nutrition in mechanically ventilated, critically ill patients and predefined subgroups.

Acknowledgment

We are greatly indebted to Rob Strack van Schijndel for his work and vision; Rob died prematurely in 2009.

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