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The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients

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This study was presented at the ESPEN 2007 Congress as a pilot study (first 50 patients) and won the best scientific abstract award.

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Abstract *Purpose:* To determine whether nutritional support guided by repeated measurements of resting energy requirements improves the outcome of critically ill patients. *Methods:* This was a prospective, randomized, single-center, pilot clinical trial conducted in an adult general intensive care (ICU) unit. The study population comprised mechanically ventilated patients ($n = 130$) expected to stay in ICU more than 3 days. Patients were randomized to receive enteral nutrition (EN) with an energy target determined either (1) by repeated indirect calorimetry measurements (study group, $n = 56$), or (2) according to 25 kcal/kg/day (control group, $n = 56$). EN was supplemented with parenteral nutrition when required. *Results:* The primary outcome was hospital mortality. Measured pre-study resting energy expenditure (REE) was similar in both groups (1,976 ± 468 vs. 1,838 ± 468 kcal, $p = 0.6$). Patients in the study group had a higher mean energy (2,086 ± 460 vs. 1,480 ± 356 kcal/day, $p = 0.01$) and protein intake (76 ± 16 vs. 53 ± 16 g/day, $p = 0.01$). There was a trend towards an improved hospital mortality in the intention to treat group (21/65 patients, 32.3% vs. 31/65 patients, 47.7%, $p = 0.058$) whereas length of ventilation (16.1 ± 14.7 vs. 10.5 ± 8.3 days, $p = 0.03$) and ICU stay (17.2 ± 14.6 vs. 11.7 ± 8.4, $p = 0.04$) were increased. *Conclusions:* In this single-center pilot study a bundle comprising actively supervised nutritional intervention and providing near target energy requirements based on repeated energy measurements was achievable in a general ICU and may be associated with lower hospital mortality.

Keywords Nutritional support · Critically ill · Indirect calorimetry · Energy balance

Introduction

Recently, guidelines have recommended the use of nutritional support, preferably by the enteral route, within the first 24 h of admission where this is possible, for critically ill patients in the intensive care unit (ICU) [1–4]. Optimal energy requirement remains an unresolved issue [1, 5]. Large energy deficits may result in increased infectious complications and prolong mechanical ventilation as well as ICU stay [6–8]. Factors contributing to the energy debt include the absence of feeding protocols, physical factors interfering with nutritional delivery such as impaired gastric motility, and frequent interruptions due to the presence of diarrhea or the performance of procedures, such as surgery or radiological examinations [9–11] as well as the inadequate assessment of ongoing and changing nutritional needs. Although energy requirements are most accurately assessed by measuring resting energy expenditure (REE) using indirect calorimetry (IC) [12], this method is not widely available or employed [13]. Instead, predictive equations like the consensus statement of the American College of Chest Physicians (ACCP) recommendation, which calculates REE as a multiple of total body weight [14], are usually used. However, these equations appear to be less accurate when compared to IC [15].

The aim of the present pilot study was to determine whether the outcome of critically ill patients is improved when nutritional support is guided by repeated measurements of REE compared to a single, initial weight-based measurement.

Materials and methods

Subjects

This single-center pilot study was conducted in the 12-bed general intensive care department of the Rabin Medical Center, a tertiary-care, university-affiliated hospital, over a 14-month period. The study was approved by the local institutional review board, and prior to randomization, written informed consent was obtained from the patient, an authorized next of kin in the first period of the study (May 2007–December 2007), and thereafter from either the patient or, where this was not possible, from an independent physician advocate. All patients aged over 18 years admitted to the ICU who were mechanically ventilated and expected to have an ICU stay of more than 3 days were eligible for the study. The main exclusion criteria were requirement for inspired oxygen content (FiO_2) greater than 0.6, air leaks through chest drains, inhaled nitric oxide therapy and continuous renal replacement therapy (CRRT), and pregnancy. In addition, patients suffering from significant head trauma (GCS < 8), severe liver disease (Child–Pugh score C), or after open-heart surgery were also excluded because the length of stay is frequently related to the underlying condition.

Study protocol and techniques

Our primary outcome was to determine whether nutritional support guided by repeated REE measurements improved hospital survival of critically ill patients compared to a single, initial weight-based measurement. Secondary outcomes included (1) length of mechanical ventilation, of ICU and hospital stay; ICU mortality; (2) development of new pressure sores; (3) requirement for unplanned surgery and surgical complications; (4) the incidence of renal impairment, defined by an increase of serum creatinine greater than 1.2 mg/dL or requirement for renal replacement therapy; and (5) the incidence of new onset liver impairment, defined by an increase of total bilirubin greater than 1.2 mg/dL; and (6) infectious complications defined according to the International Sepsis Forum definition of infections in the ICU [16] (see "Appendix"). The presence of infection was determined retrospectively and independently by two of the investigators (RA and SL), and included all infections occurring at least 48 h after enrollment.

Patients eligible were randomly assigned by a concealed, computer-generated program to 2 groups, the tight calorie and the control group, within 48 h of ICU admission. The tight calorie group comprised patients who received calories with an energy goal determined by repeated REE measurements using IC (Deltatrac II Metabolic Monitor, Datex-Engstrom, Finland). The control group comprised patients with an energy goal based on a single determination of a weight-based formula (pre-admission weight obtained from either the patient or a close family member) at the time of patient recruitment, viz. 25 kcal/kg/day [14]. The study was not blinded. Before each measurement, the metabolic monitor was allowed to warm up for 60 min, and then gas and pressure calibrations were performed by an experienced nurse or dietician, using air and a manufactured mixture (5% CO_2 and 95% O_2). The REE was recorded after a 30- to 60-min non-fasting steady state. No correction factor was applied for fasting and the values obtained were not rounded. EN was commenced at an initial rate of 20 mL/h, and increased by 20 mL/h every 6 h in the absence of significant gastric residuals (i.e., <500 mL), with the aim of reaching the energy goal within 24 h of entering the study. In the study group, the dietician in charge of the study was responsible for ensuring the achievement of energy targets, whereas in the control group this was the responsibility of the ward staff according to the routine nutrition protocol. Supplemental PN was used to make up the energy shortfall. IC measurements were repeated in both groups every 48 h. Results were used to adjust the

energy prescription in the study group, whereas the energy prescription in the control group was kept constant according to the initial assessment of energy requirements. Energy data were collected over a 24-h period from 0600 hours. The EN formulae used included Jevity 1.0 (1.06 kcal/mL, 44 g/L protein, Abbott Laboratories); Osmolite (1.06 kcal/mL, 37 g/L protein, Abbott Laboratories). Nutren 2.0 (2 kcal/mL, 80 g/L protein, Nestle) was preferentially used as the initial EN support where the energy target was greater than 1,500 kcal/day. The parenteral nutrition formula used was OClinomel N6-900E (containing 1,000 kcal/L and 34 g/L protein; Baxter). Nutrition was administered according to the calorie goal whereas protein intake was dependent on the rate and composition of EN or parenteral nutrition provided. Continuous intravenous (IV) insulin therapy was given to maintain blood glucose levels below 150 mg/dL.

Data collection

The following data were collected in all patients: demographic characteristics, including age, sex, weight, height, body mass index (BMI); admission illness severity as assessed by the APACHE II score [17]; admission category (surgical, trauma, or medical); daily SOFA score [18]; and daily mean blood glucose level. Energy and protein intake from all sources, including nutritional support, intravenous fluids, and therapeutic agents (e.g., propofol), were collected using a data management system (Metavision, *i*MD*soft*, Israel). Non-nutritional calories were not included in the target prescription, but they were included in the calculation of energy intake and energy balance. Energy balances were assessed daily, i.e., daily energy balance, and at either day 14 or discharge from the ICU, i.e., cumulative energy balance. After 14 days, energy intake was continued according to the last REE determination. Maximum negative energy balance was defined as the most negative cumulative balance observed during the study period. Protein intake was also calculated on a daily basis.

Statistical analysis

The Student's *t* test was used when comparisons were made for parametric data. Non-parametric data were analyzed with the Mann–Whitney *U* test. Chi-square or Fisher's exact test was used to test differences between categorical variables. Correlations between energy balances and complications were tested using one-way analysis of variance (ANOVA) between groups and within groups. ANOVA was also used to determine whether energy targets in the study group were changing over time. Survival analysis was performed with the Kaplan–Meier method. Calculations were performed using SPSS software (version 12.0, SPSS, Chicago, IL). Results are expressed as mean ± standard deviation. Separate analyses were performed for all patients initially included in the study ($n = 130$), i.e., intention to treat (ITT) analysis, from which patients were excluded due to a short ICU stay, protocol violations, or inability to achieve the measured energy expenditure using parenteral nutrition. This latter group defined the per protocol group ($n = 112$). A p level less than 0.05 was considered as significant.

Results

Patient characteristics

In total, 944 patients were screened, of whom 130 patients were eligible for the study. The main reasons for non-inclusion were expected short hospitalization ($n = 316$), not ventilated ($n = 50$), and requiring nitric oxide inhalation ($n = 55$). Sixteen patients were excluded as their ICU stay was less than 3 days, 1 was excluded because of protocol violation (elevated liver function tests not

Table 1 Baseline characteristics of all randomized patients ($n = 130$)

Variable	Study group ($n = 65$)	Control group ($n = 65$)	p value
Age (years)	59 ± 18	62 ± 17	0.38
Male sex, *n* (%)	35 (54)	41 (63)	0.37
Weight (kg)	79.8 ± 19.5	78 ± 18.2	0.57
BMI (kg/m^2)	27.8 ± 6.3	27.4 ± 7.3	0.83
SOFA score day 1	6.4 ± 2.9	6.6 ± 3.5	0.65
APACHE II score	22.1 ± 7.4	22.4 ± 6.8	0.84
Admission category			0.73
Surgical, *n* (%)	14 (22)	17 (26)	
Multiple trauma, *n* (%)	15 (23)	12 (19)	
Medical, *n* (%)	36 (55)	36 (55)	

BMI body mass index, *SOFA* sequential organ failure assessment score, *APACHE* acute physiology and chronic health evaluation score

Table 2 Patient diagnoses according to medical, surgical, and trauma categories for all patients ($n = 130$)

Variable	Study group ($n = 65$)	Control group ($n = 65$)
Medical category	36	36
Acute lung injury	13	18
Severe sepsis	16	13
Bacterial endocarditis	2	1
Acute epiglottitis	1	
Other	4	4
Surgical category	14	17
Peritonitis	4	3
Short bowel syndrome	2	2
Other	8	12
Trauma category	15	12

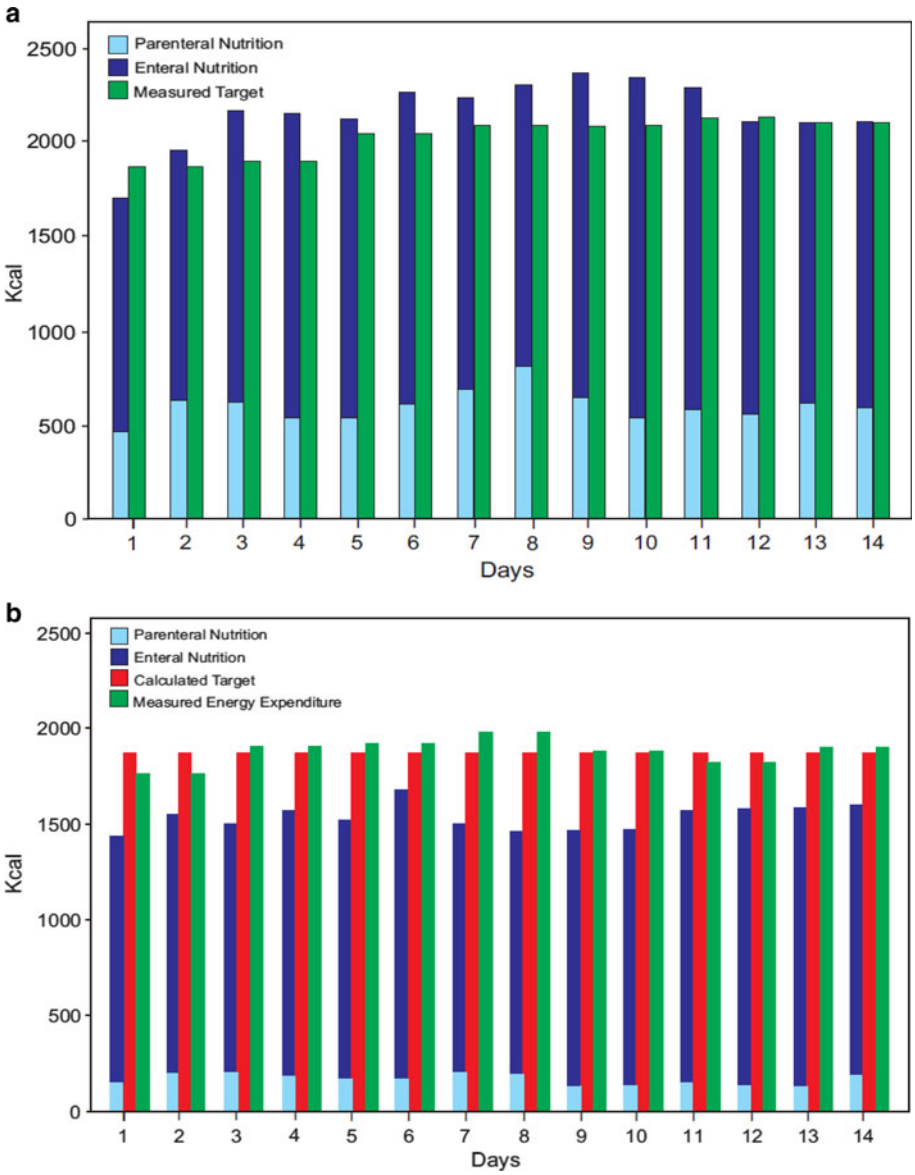

Fig. 1 **a** Study group—mean daily measured target based on indirect calorimetry compared to mean daily energy delivered from both enteral and parenteral sources. The measured energy expenditure values were significantly different ($p < 0.008$) from day to day in the first 10 days. **b** Control group—mean daily measured and calculated target based on weight-based formula compared to mean daily energy delivered from both enteral and parenteral sources. The measured energy expenditure values were significantly different ($p < 0.008$) from day to day in the first 10 days

diagnosed at inclusion), and another as the measured energy expenditure could not be achieved using parenteral nutrition (>5,000 kcal). Of the remaining patients, 56 were randomized to each group. Patient characteristics and diagnoses are given in Tables 1 and 2, respectively. There were no significant differences between the groups regarding these characteristics.

Energy and protein parameters

Figure 1 shows the mean daily energy targets for both groups (study group as assessed by IC and control group as assessed by the weight-based formula) compared to the daily energy intake from both EN and PN over the study period. In the study group, the energy targets assessed by IC changed significantly ($p < 0.008$) over time for the first 10 days studied. Patients received higher energy intake from both sources compared to measured daily targets over the entire period. In the control group, energy intake was consistently lower than calculated energy targets over the entire period. Mean energy values for the whole study are shown in Table 3. Mean measured REE was not significantly different between the 2 groups. Mean daily calorie intake was significantly higher in the study group ($p = 0.001$), due to more energy from both EN ($p = 0.013$) and PN ($p = 0.03$). In addition, significantly more patients in the study group received PN during the first 3 days of the study (17 vs. 6; $p = 0.02$).

The mean daily energy balance was significantly more positive in the study group ($p = 0.001$). This was associated with a positive total cumulative energy balance and

Table 3 Summary of energy and protein parameters during the study period (means of all values during the ICU stay) in the per protocol group ($n = 112$)

Parameter	Study group ($n = 56$)	Control group ($n = 56$)	p
Mean REE (kcal/day)	1,976 ± 468	1,838 ± 468	0.6
Mean energy delivered/day (kcal/day)	2,086 ± 460	1,480 ± 356	0.01
Mean enterally delivered energy/day (kcal/day)	1,515 ± 756	1,316 ± 456	0.09
Mean parenterally delivered energy/day (kcal/day)	571 ± 754	164 ± 294	0.001
Route of administration (n)			
Enteral	34	48	
Parenteral	3	1	
Enteral and parenteral	19	7	
Mean protein delivered/day (g/day)	76 ± 16	53 ± 16	0.001
Mean daily energy balance (kcal)	186 ± 206	−312 ± 481	0.001
Cumulative energy balance (kcal)	2,008 ± 2,177	−3,550 ± 4,591	0.01
Maximum negative energy balance (kcal)	15.7 ± 883	−3,895 ± 4,144	0.01
Daily mean blood glucose (mg/dL)	119.6 ± 21.8	127.3 ± 33.7	0.82

REE resting energy expenditure, *kcal* kilocalories

maximum negative energy balance in the study group, whereas both these balances were negative in the control group ($p = 0.001$ for both balances). Mean daily protein intake was significantly higher in the study group ($p = 0.001$) whereas the mean daily blood glucose levels were similar in the 2 groups ($p = 0.15$).

Primary outcome

A Kaplan–Meier curve for intention to treat ($n = 130$) demonstrated a trend toward a lower mortality in the study group ($p = 0.058$; Fig. 2a). A Kaplan–Meier curve for the "per protocol" group shows that hospital mortality was significantly lower in the study group (16/56 patients, 28.5% vs. 27/56 patients, 48.2%; $p = 0.023$; Fig. 2b). Survival at 60 days was 57.9 ± 9.9% in the study group and 48.1 ± 7.6% in the control group ($p = 0.023$).

Secondary outcomes

As shown in Table 4, ICU mortality was not significantly different between the 2 groups (24.6 vs. 26.2%; $p = 0.64$). Length of ventilation and of ICU stay were both significantly longer in the study group ($p = 0.01$ and $p = 0.02$, respectively) and total infection rate ($p < 0.05$) was higher. There was a trend for a higher incidence of VAP in the study group ($p = 0.08$). SOFA score was significantly lower in the study group at day 3 compared to the control group (5.44 ± 2.76 vs. 7.04 ± 4.25, $p = 0.027$).

Discussion

In this prospective, randomized, controlled pilot trial, we have shown that nutritional support adjusted by repeated measures of energy expenditure resulted in significantly lower hospital mortality for critically ill patients. We also observed that these patients had a longer ICU stay and duration of mechanical ventilation.

In previous studies such as the ACCEPT [19] and ANZICS studies [20], patients in the intervention arm received nutritional support according to evidence-based algorithms. In both studies, this resulted in improved nutritional delivery: more days of EN in the ACCEPT study ($p = 0.042$), and earlier nutrition start ($p < 0.001$) and more frequent achievement of caloric goals ($p = 0.03$) in the ANZICS study. Despite this, the authors did not detect any significant change in hospital mortality. The method used to determine energy requirements in ACCEPT/ANZICS studies was weight-based and intake of 1,264 and 1,241 kcal/patient/day was achieved, respectively. Our study measured REE and achieved an energy intake of 2,086 ± 460 kcal/day.

Both early delivery and provision of adequate amounts of energy may be important in determining outcome. Others have reported that the supply of early nutritional support alone had no positive effect on outcome whereas increasing calories to more than 1,500 kcal resulted in reduced hospital mortality [21]. In our prospective, randomized, interventional pilot study, the study group received significantly more calories than the control group (2,086 ± 460 vs. 1,480 ± 356 kcal/day; $p = 0.01$). It thus appears that the improved energy delivery in the study group was a function of both determining a defined and dynamic energy goal, i.e., the repeated REE measurements, and of the intensity of the resulting intervention required to achieve this goal. The improved energy delivery may have resulted in a significant clinical outcome, namely a lower hospital mortality in the study group. We used hospital mortality as an end-point rather than ICU mortality because nutritional interventions may not be expected to impact on short-term ICU variables but require more time to become apparent.

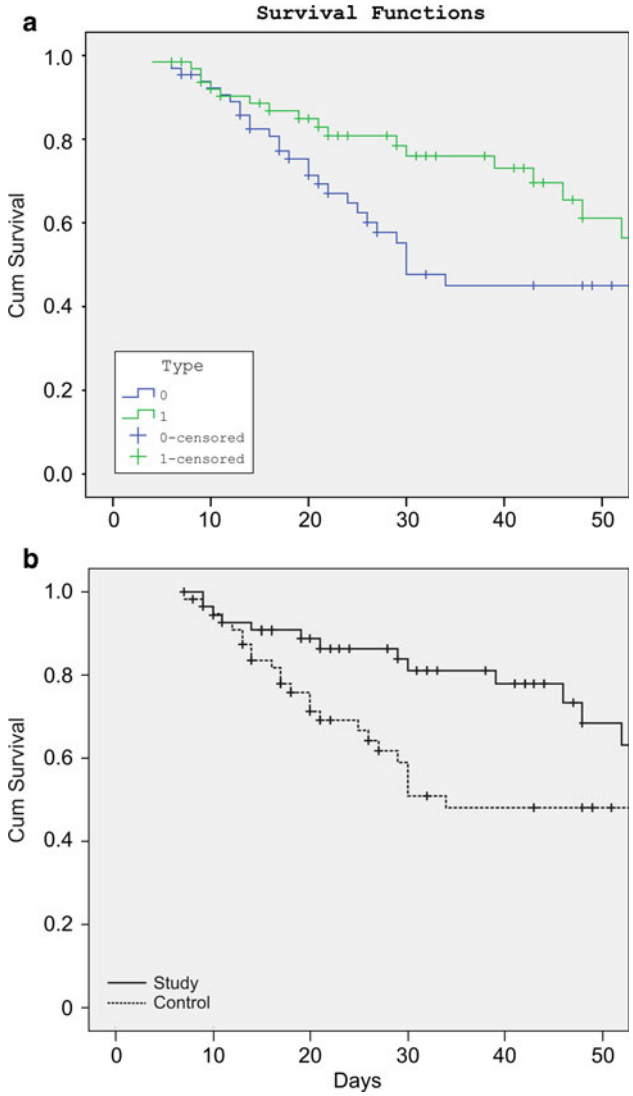

Fig. 2 **a** Kaplan–Meier curves for hospital discharge mortality for all patients (intention to treat) ($n = 130$). The study group showed an improved outcome compared to the control group (Breslow, $p = 0.058$). **b** Kaplan–Meier curves for hospital discharge mortality for all patients (per protocol) ($n = 112$). The study group showed an improved outcome compared to the control group (Breslow, $p = 0.023$)

Table 4 Secondary outcomes for all patients ($n = 130$). Infectious complications are expressed in absolute numbers and percentage between brackets

Variable	Study group ($n = 65$)	Control group ($n = 65$)	p value
ICU mortality (%)	24.60%	26.20%	1.0
Duration ventilation (days)			
Mean	16.1 ± 14.7	10.5 ± 8.3	0.03
Median (range)	12.5 (1–82)	9 (1–33)	
Duration ICU stay (days)			
Mean	17.2 ± 14.6	11.7 ± 8.4	0.04
Median (range)	14 (1–84)	10 (0.5–35)	
Duration hospital stay (days)			
Mean	33.8 ± 22.9	31.8 ± 27.3	0.33
Median (range)	29 (4–101)	21 (4–142)	
Infectious complications (n)	37	20	0.05
VAP (%)	18 (27.7%)	9 (13.8%)	0.08
Bacteremia (%)	13 (20.0%)	8 (12.3%)	0.33
Urinary tract infections (%)	0	1 (1.5%)	1.0
Wound infections (%)	5 (7.7%)	1 (1.5%)	0.21
Abdominal infections (%)	1 (1.5%)	1 (1.5%)	1.0
New pressure ulcers (%)	26 (40.0%)	20 (30.8%)	0.34
Unplanned surgery and surgical complications (%)	4 (6.2%)	3 (4.6%)	1.0
Renal impairment[a] & requirement for RRT (%)	14 (21.6%)	10 (15.4%)	0.49
Liver impairment[b] (%)	8 (12.3%)	10 (15.4%)	0.8

VAP ventilator-associated pneumonia, *RRT* renal replacement therapy

[a] Serum creatinine >1.2 mg/dL

[b] Serum bilirubin >1.2 mg/dL

The study group received a significantly higher intake of protein, related solely to the nutrition composition based on the calories received. Strack van Schijndel et al. [22] observed that reaching an energy goal guided by IC and a protein goal of 1.2 g/kg in ICU patients reduced ICU and hospital mortality. Alberda et al. [23] observed that increasing both calorie intake and protein intake were associated with improved 60-day survival.

Previous studies of EN in the ICU have stressed the difficulties associated with achieving nutritional targets [9–11]. Combining EN and PN [24, 25], as we did in our study, could help reaching the energy target. A recent meta-analysis demonstrated no increased mortality with PN [26]. Significantly more patients in our study group received PN during the first 3 days compared to the control group (17 vs. 6; $p = 0.02$), allowing us to achieve energy goals. Further prospective, randomized trials are required to assess the effect of such combined therapy on clinical outcomes.

Tight calorie control as achieved in our pilot study represents a balance between underfeeding on the one hand and overfeeding on the other. The frequency and dangers of underfeeding have been elaborated above. However, overfeeding, too, may be seen in critically ill patients, and may be associated with complications such as increased infectious rate [27], liver dysfunction [28],

hyperthermia, hyperglycemia, hypertriglyceridemia, and fluid overload [29]. The extent to which additional calories are administered intravenously from various sources, including PN, dextrose infusions, and medications such as propofol, is not always appreciated. We used a bedside computerized information system (CIS) to obtain a more complete assessment of energy balance. In general, improvement of data acquisition using such a system has been demonstrated to improve the quality of medical documentation, improve the quality of the data, and decrease the workload necessary to achieve these ends [8, 30, 31]. Regarding nutrition in particular, in burn patients CIS use has been shown to favor standardization of nutritional care and monitoring, and improve follow-up so that nutrient delivery was closer to target values, thus increasing quality of care [32]. Using this careful monitoring, we observed no manifestations of overfeeding in our patients.

There was no difference in the occurrence of new organ failure, or ICU mortality between the study and control groups, despite the significant differences in energy balance, maybe because the negative cumulative energy balance in our study was not large (i.e., $-3{,}486 \pm 4{,}233$ kcal). Although, as previously mentioned, studies have shown that incurring a negative energy balance may result in increased infectious complications [6] and even mortality [22], these were associated with large energy deficits, viz. $-10{,}000$ kcal at the end of the first week. The present study did reveal a prolonged duration of mechanical ventilation and thus of ICU stay in the study group. The reason(s) for this is (are) not readily evident. A possible cause includes the increased calorie-related metabolic load in the study group. In addition, we found a significant increase in infection rate, with a trend for an increased incidence of VAP in the study group (27.7 vs. 13.8%; $p = 0.08$). This may be related to the early delivery and increased amount of EN the study patients received. Similar findings were reported in a retrospective study by Artinian et al. [33] who showed that early enteral feeding was associated with improved ICU and hospital mortality despite an increased risk of VAP.

Our study has limitations. Tight calorie control is ideally (and possibly only) achieved using two technologies which must be familiar to the department, namely a CIS and IC. The present single-center study was performed in a department where IC is routinely available and has been used over several years as the standard of care for assessing nutritional requirements. Thus there was no need to overcome learning or technical problems associated with the implementation of this technique. Secondly, nutrition was not protein targeted, but the amount of protein was determined by the rate of EN or parenteral nutrition provided. This resulted in patients receiving below the currently recommended levels. Thirdly, a population of severely ill patients were excluded as they were not eligible for IC. Therefore the conclusions of this study are relevant only for the particular study population. However, the patients included in the study are certainly representative of a multidisciplinary intensive care department treating severely ill patients, as evidenced by the high mean APACHE II score of recruited patients.

In conclusion, we have shown in a single-center pilot study that a bundle comprising actively supervised nutritional intervention and providing near target energy requirements based on repeated energy measurements using both EN and PN was achievable in a general ICU and may be associated with lower hospital mortality. However, this was also associated with prolonged duration of mechanical ventilation and ICU stay. We believe that these findings should be confirmed by larger, prospective, multi-center studies.

Appendix: Infectious complications defined according to the International Sepsis Forum definition of infections in the ICU [16]

1. Ventilator-associated pneumonia (presence of fever, elevated white blood cell count, purulent sputum, abnormal chest radiograph, and the presence of potential pathogens in lower respiratory tract secretions)
2. Blood stream infections (either primary, in the presence of a recognized pathogen cultured from one or more blood cultures where the organism cultured is not related to an infection at another site, or secondary, where an organism different from common skin contaminants is isolated from one or more blood cultures and is related to an infection with the same organism at another site)
3. Intra-abdominal infections (either primary, in the absence of intra-abdominal derangements, secondary, in the presence of intra-abdominal derangements such as perforation, or tertiary, where peritonitis persists for more than 48 h after apparent successful treatment of primary or secondary peritonitis)
4. Wound infections (the isolation by culture or gram stain of a microorganism from a wound or skin lesion that has drained pus)
5. Urinary tract infections (in the presence of fever greater than 38°C, localized tenderness over one or both kidneys, and pyuria).

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