Energy metabolism, nitrogen balance, and substrate utilization in critically ill children[1–3]

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ABSTRACT

Background: Critically ill patients are characterized by a hypermetabolic state, a catabolic response, higher nutritional needs, and a decreased capacity for utilization of parenteral substrate.

Objective: We sought to analyze the relation between a patient's metabolic state and their nutritional intake, substrate utilization, and nitrogen balance (NB) in mechanically ventilated, critically ill children receiving parenteral nutrition.

Design: This was a cross-sectional study in which resting energy expenditure (REE) and NB were measured and substrate utilization and the metabolic index (MI) ratio (REE/expected energy requirements) were calculated.

Results: Thirty-three children (mean age: 5 y) participated. Their average REE was 0.23 ± 0.10 MJ·kg^{-1}·d^{-1} and their average MI was 1.2 ± 0.5. Mean energy intake, protein intake, and NB were 0.25 ± 0.14 MJ·kg^{-1}·d^{-1}, 2.1 ± 1 g·kg^{-1}·d^{-1}, and -89 ± 166 mg·kg^{-1}·d^{-1}, respectively. Patients with an MI >1.1 ($n = 19$) had a higher fat oxidation than did patients with an MI <1.1 ($n = 14$; $P < 0.05$). Patients with lipogenesis ($n = 13$) had a higher carbohydrate intake than did patients without lipogenesis ($n = 20$; $P < 0.05$). Patients with a positive NB ($n = 12$) had a higher protein intake than did patients with a negative NB ($n = 21$; $P < 0.001$) and lower protein oxidation ($P < 0.01$).

Conclusions: Critically ill children are hypermetabolic and in negative NB. In this population, fat is used preferentially for oxidation and carbohydrate is utilized poorly. A high carbohydrate intake was associated with lipogenesis and less fat oxidation, a negative NB was associated with high oxidation rates for protein, and a high protein intake was associated with a positive NB. *Am J Clin Nutr* 2001;74:664–9.

KEY WORDS Energy expenditure, nitrogen balance, substrate oxidation, pediatrics, mechanical ventilation, critically ill patients

INTRODUCTION

The provision of nutritional and metabolic support has become an essential component in the care of critically ill patients. Several reports showed that inadequate provision of nutrients is associated with increased physiologic instability and increased care of critically ill patients (1, 2).

Studies that used indirect calorimetry to measure energy metabolism showed that energy expenditure in critically ill patients is higher than expected by a factor of 1.2–1.5 (3–7). In addition, these patients exhibited an increased catabolic response that is proportional to the degree of metabolic insult. Multiple studies in critically ill adults and children showed that this population of patients has not only higher nutritional needs (8–11), but also has a decreased capacity to maximize the use of different parenteral substrates (12–15).

Adequate energy intake in critically ill children is essential to provide sufficient substrates for metabolic functions during the acute phase of the disease process, in addition to providing for new growth, a factor of utmost importance in the pediatric patient. However, excessive amounts of energy, particularly in the form of glucose, can be deleterious to the patient and can result in lipogenesis, increased carbon dioxide production, hepatic steatosis, and liver dysfunction (16, 17).

The purpose of the present study was to analyze the relation between a patient's metabolic state and their nutritional intake, substrate utilization, and nitrogen balance in a population of critically ill children receiving total parenteral nutrition.

SUBJECTS AND METHODS

This cross-sectional study measured nitrogen balance and substrate utilization in 33 critically ill children receiving parenteral nutrition while on mechanical ventilation. All subjects were hospitalized in the pediatric intensive care unit of Texas Children's Hospital. The protocol was approved by the Institutional Review Board for studies involving human subjects and informed parental consent was obtained before the study.

Resting energy expenditure (REE) was measured by indirect calorimetry with a spectrometer-based metabolic cart. We published validation data for the use of this cart in mechanically

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ventilated children (7). The expected energy requirements (EER) of healthy children were obtained from Talbot's tables (18). A hypermetabolic state was defined as a metabolic index (REE/EER) >1.1 (8). The use of this technique and clinical protocol was described in detail previously (19).

Data collected included age, weight, diagnosis, length of stay in intensive care, and duration of ventilatory support at the time of the study. The Pediatric Risk of Mortality (PRISM) score was obtained. The PRISM score is a measure of illness severity calculated from physiologic and laboratory information from 14 variables and is based on the observation that the amount and extent of physiologic dysfunction is related to the patient's mortality (20). The Therapeutic Intervention Scoring System (TISS) score was also obtained. It is calculated from 76 therapeutic and monitoring modalities that reflect physician and nursing interventions (21).

The ventilator settings that were recorded included the following: inspired oxygen concentration (FiO_2), positive end-expiratory pressure, tidal volume (V_T), ventilator rate, peak inspiratory pressure, and mean airway pressure (P_{aw}). The oxygenation index [($P_{aw} \times FiO_2 \times 100$)/partial pressure of oxygen in the blood] and the ventilation index [(partial pressure of carbon dioxide in the blood × peak inspiratory pressure × ventilator rate)/100] were also calculated.

All patients were receiving intravenous nutrition at the time of the study and for the previous 48 h before the measurements were performed. According to our parenteral nutrition support hospital protocol, all patients aged <1 y received a parenteral amino acid mixture with 30% branched-chain amino acids (TrophAmine; MCGAW, Irvine, CA). Patients aged >1 y received a parenteral amino acid mixture with 24.6% branched-chain amino acids (Aminosyn; Abbott Laboratories, Abbott Park, IL). Total energy intake was calculated based on the components of the parenteral formulation. Nitrogen balance was calculated based on nitrogen intake and on total urinary nitrogen in a 24-h urine collection measured by use of the Kjeldahl method (22). The nonprotein respiratory quotient (npRQ) and the utilization rates of carbohydrate, protein, and fat were calculated by using the Conzolazio formulas (23).

For the purpose of the present study, a high carbohydrate intake was defined as a continuous glucose infusion >8 $mg \cdot kg^{-1} \cdot min^{-1}$ (14) and lipogenesis or net fat synthesis was defined as an npRQ >1.00 (24). Statistical analysis was calculated by using the Mann-Whitney *U* test and the Spearman rank-order correlation coefficient (STAT VIEW 5; SAS Institute, Inc, Cary, NC). Values are presented as means ± SDs.

RESULTS

Thirty-three patients (18 women and 15 men) participated in the study. The patient's mean age was 5.5 ± 5.3 y (range: 0.4–17 y) and their mean weight was 21 ± 17 kg (range: 5.5–66 kg). The diagnoses were as follows: 9 subjects had bacterial sepsis, 7 subjects had pneumonia and sepsis, 7 subjects were in a postoperative state for gastrointestinal conditions, 4 subjects had septicemia and malignancy, 2 subjects had erythema multiforme, 2 subjects had *Pneumocystis carinii* pneumonia, 1 subject had a systemic fungal infection, and 1 subject had respiratory failure and pulmonary eosinophilia. The mean length of stay in the intensive care unit at the time of the study was 14 ± 26 d, with a mean mechanical ventilation time of 13 ± 26 d. The mean PRISM score on the day of the study was 10 ± 7 points, with a mean TISS score on the day of the study of 31 ± 6 points. The subjects' mean body temperature during the measurements was 37.3 ± 0.6°C. Three subjects had body temperatures ≤36.5°C. No subjects had a body temperature =38.5°C. The mean ventilator parameters were as follows: FiO_2 of 0.51 ± 0.10, positive end-expiratory pressure of 8 ± 4 cm H_2O, V_T of 11 ± 5 mL/kg, ventilator rate of 19 ± 7 breaths/min, peak inspiratory pressure of 43 ± 16 cm H_2O, and a P_{aw} of 14 ± 6 cm H_2O. The mean oxygenation index was 9 ± 8 and the mean ventilation index was 45 ± 31.

The average measured energy expenditure was 0.23 ± 0.10 $MJ \cdot kg^{-1} \cdot d^{-1}$ and the average expected energy requirement was 0.19 ± 0.04 $MJ \cdot kg \cdot^{-1} \cdot d^{-1}$. This resulted in an average metabolic index value of 1.2 ± 0.74. The mean energy intake was 0.25 ± 0.14 $MJ \cdot kg^{-1} \cdot d^{-1}$, with a mean carbohydrate intake of 10 ± 5 $g \cdot kg^{-1} \cdot d^{-1}$, a mean protein intake of 2.1 ± 1 $g \cdot kg^{-1} \cdot d^{-1}$ (95% CI: 1.7, 2.4), and a mean fat intake of 1.4 ± 1.3 $g \cdot kg^{-1} \cdot d^{-1}$. The total energy-to-nitrogen ratio was 190 ± 84. The nonprotein energy-to-nitrogen ratio was 165 ± 84. The average total urinary nitrogen excretion was 347 ± 142 $mg \cdot kg^{-1} \cdot d^{-1}$, with an average nitrogen balance of −89 ± 166 $mg \cdot kg^{-1} \cdot d^{-1}$. The average nitrogen balance was −60 ± 167 $mg \cdot kg^{-1} d^{-1}$ in patients who received TrophAmine (n = 8) compared with −98 ± 167 $mg \cdot kg^{-1} \cdot d^{-1}$ in patients who received Aminosyn (n = 25; P = 0.14). The ratio of nitrogen balance index to weight did not show a significant correlation with the ratio of total energy to nitrogen (r = 0.14; P = 0.40) or with a ratio of nonprotein energy to nitrogen (r = 0.14, P = 0.40).

The average carbohydrate oxidation was 0.119 ± 0.12 g/min, with a mean protein oxidation of 0.032 ± 0.03 g/min and a mean fat oxidation of 0.006 ± 0.06 g/min. The average npRQ was 1.01 ± 0.31.

The mean REE/kg body in hypermetabolic patients (n = 19) was 0.28 ± 0.10 $MJ \cdot kg^{1} \cdot d^{-1}$ compared with 0.16 ± 0.05 $MJ \cdot kg^{-1} \cdot d^{-1}$ in the group of patients with a metabolic index <1.1 (n = 14; P < 0.0005). The correlation between REE/kg and metabolic index was significant (r = 0.79, P < 0.0001). The hypermetabolic patients had a lower ratio of energy received (0.81 ± 0.35) in relation to REE than did patients with a metabolic index <1.1 (1.84 ± 0.72; P < 0.0001). The average npRQ in the hypermetabolic patients was 0.86 ± 0.22 compared with 1.21 ± 0.29 in the group of patients with a metabolic index <1.1 (P < 0.005). The correlation between npRQ and the metabolic index was significant (r = −0.35, P < 0.05). The average fat oxidation in the hypermetabolic patients was 27 ± 70 mg/min compared with −22 ± 29 mg/min in the group of patients with a metabolic index <1.1 (P < 0.005) (**Figure 1**). The correlation between fat oxidation and metabolic index was significant (r = 0.44, P < 0.05).

In subjects with lipogenesis (n = 13), the average REE/kg body was 0.17 ± 0.01 $MJ \cdot kg^{-1} \cdot d^{-1}$, which was lower than the average REE/kg body of 0.26 ± 0.10 $MJ \cdot kg^{-1} \cdot d^{-1}$ (P < 0.01) in subjects without lipogenesis (n = 20). Subjects with lipogenesis had an average ratio of energy intake to REE of 1.87 ± 0.74, which was higher than the ratio of 0.84 ± 0.38 in subjects without lipogenesis. The subjects with lipogenesis had a lower fat oxidation (−39 ± 26 mg/min) than did subjects without lipogenesis (36 ± 60 mg/min; P < 0.0001). The correlation between fat oxidation and npRQ was significant (r = −0.92, P < 0.0001). Subjects with lipogenesis had a higher average carbohydrate

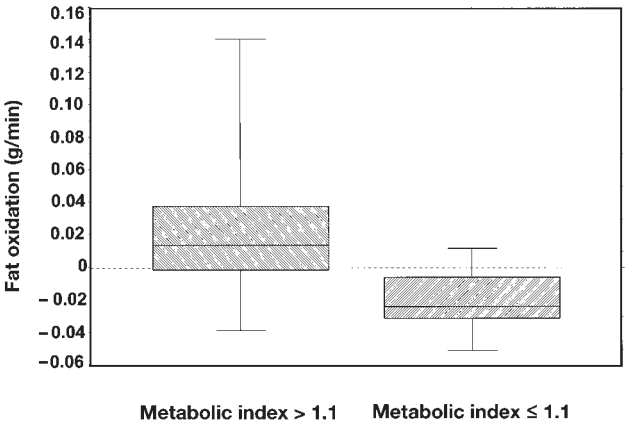

FIGURE 1. Box plot showing the difference ($P < 0.005$) in fat oxidation between subjects with a metabolic index >1.1 ($n = 19$) and those with a metabolic index <1.1 ($n = 14$). The line through the boxes denotes the median, and the variance bars denote the 90th and 10th percentiles.

intake (8.5 $mg \cdot kg^{-1} \cdot min^{-1}$) than did subjects without lipogenesis (6.1 $mg \cdot kg^{-1} \cdot min^{-1}$; $P < 0.05$) (**Figure 2**). The correlation between carbohydrate intake and npRQ was significant ($r = 0.37$, $P < 0.05$). The amount of glucose infusion (in $mg \cdot kg^{-1} \cdot min^{-1}$) was not significantly correlated with carbohydrate oxidation (in $g \cdot kg^{-1} \cdot d^{-1}$) or with protein oxidation ($g \cdot kg^{-1} \cdot d^{-1}$), but did correlate with fat oxidation ($r = -0.38$, $P < 0.05$). No correlation was found between fat intake and carbohydrate, protein, or fat oxidation.

The average ratio of energy intake to REE was higher in subjects with a positive nitrogen balance (1.7 ± 0.81; $n = 12$) than in subjects with a negative nitrogen balance (0.99 ± 0.58; $n = 21$; $P < 0.005$). The correlation between nitrogen balance per kilogram and the energy-to-REE ratio was significant ($r = 0.51$, $P < 0.005$). The subjects with a positive nitrogen balance had a higher protein intake (2.8 ± 0.9 $g \cdot kg^{-1} \cdot d^{-1}$) than did subjects with a negative nitrogen balance (1.7 ± 0.7 $g \cdot kg^{-1} \cdot d^{-1}$; $P < 0.0001$). The correlation between nitrogen balance per kilogram and the ratio of the nitrogen intake index to body weight was significant ($r = 0.64$, $P < 0.0005$). The average protein oxidation was lower in subjects with a positive nitrogen balance (13 ± 5 mg/min) than in subjects with a negative nitrogen balance (42 ± 35 mg/min; $P < 0.01$) (**Figure 3**). The correlation between nitrogen balance per kilogram and protein oxidation was significant ($r = -0.72$, $P < 0.0001$).

DISCUSSION

In the present study, 33 critically ill children who received parenteral nutrition while being mechanically ventilated were hypermetabolic, with an average metabolic index of 1.2, which is similar to previously published studies in pediatric patients with conditions such as trauma, burns, and sepsis (3, 5, 6, 14).

It is important to measure energy expenditure in critically ill children because energy requirements in this population are proportional to their energy expenditure (7, 25). Our study population had an average energy intake that was >25% of their measured energy needs, which was consistent with the recommendations made by Chwals (16) of limiting the energy intake of acutely ill infants to ≥20% in excess of their metabolic needs.

Two recent studies of mechanically ventilated, critically ill children used indirect calorimetry to measure energy expenditure while the children received nutrition (26, 27). A study by Verhoeven et al (27) included 50 children who had an average energy intake of 0.24 $MJ \cdot kg^{-1} \cdot d^{-1}$, representing >14% of their measured energy needs. Joosten et al (26) studied 36 patients whose average energy intake was 0.26 $MJ \cdot kg^{-1} \cdot d^{-1}$, which was >20% of their energy needs. These findings are similar to the results of our study.

Although adequate energy intake is essential in critically ill patients, the composition of the parenteral formula is important because the patient's inefficiency in utilizing intravenous glucose and fat may result in hepatic steatosis (28, 29). It was shown in critically ill patients that net fat synthesis occurs at different levels of parenteral glucose intake, dependent on the patient's age (14, 15, 30, 31). Jones et al (31), using indirect calorimetry, studied 11 postsurgical newborns (mean age: 25 d) receiving total parenteral nutrition and concluded that net fat synthesis occurs with a glucose intake >18 $g \cdot kg^{-1} \cdot min^{-1}$ (12.5 $mg \cdot kg^{-1} \cdot min^{-1}$). In another study, by Bresson et al (30), 36 infants (mean age: 6 mo) receiving total parenteral nutrition for medical gastrointestinal diseases were studied by using indirect calorimetry. Similar results were found pertaining to net fat synthesis when glucose intakes were >12.6 $mg \cdot kg^{-1} \cdot min^{-1}$.

Studies that incorporated the use of stable-isotope glucose tracers showed different results than did studies that used indirect calorimetry, with maximal rates of glucose oxidation that were similar in all age groups ranging from adults to preterm infants (32, 33). This difference could be explained by the fact that indirect calorimetry estimates energy utilization from the algebraic sum of glucose degradation and synthesis. By contrast, isotope techniques trace the kinetics of all blood borne substrates and reflects all energy transformations that occur at the tissue level (34). In a study by Sheridan et al (14), 10 critically ill children (mean age: 5.2 y) with burns were evaluated by using a stable-isotope tracer technique (14). The authors found that maximal glucose oxidation occurred at glucose intakes of 5 $mg \cdot kg^{-1} \cdot min^{-1}$, with a subsequent and significant decrease in the fraction of exogenous glucose that was being oxidized at

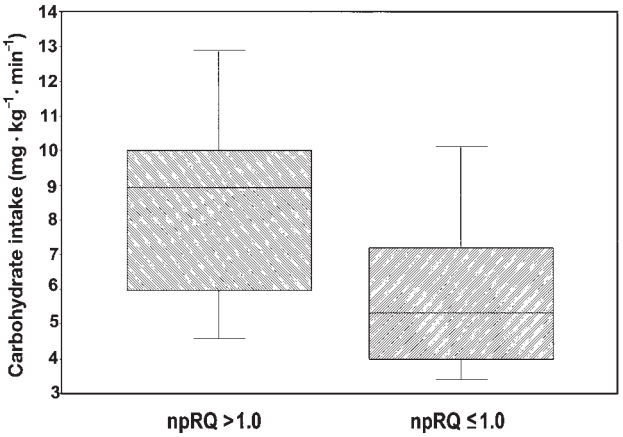

FIGURE 2. Box plot showing the difference ($P \leq 0.05$) in carbohydrate intake between subjects with lipogenesis, ie, a nonprotein respiratory quotient (npRQ) >1.0 ($n = 13$), and those patients with an npRQ ≤1.0 ($n = 20$). The line through the boxes denotes the median, and the variance bars denote the 90th and 10th percentiles.

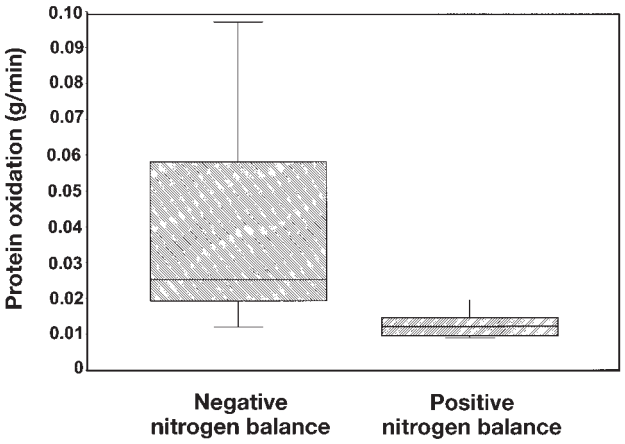

FIGURE 3. Box plot showing the difference ($P < 0.001$) in protein oxidation between patients in a negative ($n = 21$) and positive ($n = 12$) nitrogen balance. The line through the boxes denotes the median, and the variance bars denote the 90th and 10th percentiles.

intakes ≤ 8 mg·kg^{-1}·d^{-1}. In the present study, in which we used indirect calorimetry, we found that patients with lipogenesis ($n = 13$) had an average glucose intake of 8.5 mg·kg^{-1}·min^{-1} when compared with patients with an npRQ < 1.0 ($n = 20$) with average glucose intakes of 6.1 mg·kg^{-1}·min^{-1}. A more recent report by Tappy et al (15) of 16 adult surgical patients who were mechanically ventilated and who received total parenteral nutrition found that the administration of glucose at a rate of 4 mg·kg^{-1}·min^{-1} failed to suppress endogenous glucose production and gluconeogenesis (15).

It is well known that the conversion of glucose to fat elevates the RQ and reflects the proportion of substrate utilization in the body. The npRQ represents the ratio of glucose and fat utilization by excluding the participation of protein, and varies in value from 0.70–1.0, with values > 1.0 indicating net fat biosynthesis from glucose (lipogenesis). Studies of critically ill adults and children have shown that changes in the metabolic condition, or excessive energy intake in the form of glucose, modify the npRQ value (14, 15, 35, 36). In our study, 84% of the hypermetabolic subjects had an npRQ value < 1.0 and 75% of the subjects who consumed high amounts of carbohydrate had an npRQ value > 1.0.

This acute metabolic response is also characterized by increased lipolysis and fatty acid oxidation relative to glucose oxidation. The use of lipid emulsion has been advocated to avoid increasing carbon dioxide production, which is seen when glucose is administered in excess of energy requirements (12, 35, 37), but also because critically ill patients use fat preferentially as a substrate (36, 38). Our results show that hypermetabolic patients have a significantly higher rate of fat oxidation. Investigators who have conducted studies of critically ill infants and adults have concluded that intravenous fat emulsions are efficiently metabolized and significantly reduce carbon dioxide production (39, 40). In the present study a lower fat oxidation rate was seen in subjects with lipogenesis and in those who received energy in excess of measured energy needs.

The hypercatabolic state of injury or sepsis is characterized by a marked negative nitrogen balance. It has been reported that increasing the nitrogen intake in septic adult patients results in an increased nitrogen balance over a wide range of nitrogen intakes (41). Other investigators, however, have found that nitrogen intakes > 200 mg·kg^{-1}·d^{-1} have little additional effect (42). In the present study, subjects were, on average, in a negative nitrogen balance, with a mean nitrogen intake of 334 mg·kg^{-1}·d^{-1} (95% CI: 279, 388) with all subjects in a negative nitrogen balance receiving an average nitrogen intake of 270 mg·kg^{-1}·d^{-1}.

Several studies have reported improved nitrogen balance in critically ill patients receiving parenteral nutrition solutions enriched with 45–50% branched-chain amino acids (43–45) when compared with patients receiving a nutrition solution containing 15–25% branched-chain amino acids. In this study we did not see significant differences in nitrogen balance between patients receiving 30% compared with 24.6% branched-chain amino acid concentrations, possibly because the difference in content was not enough to reflect a significant difference in nitrogen balance.

There is limited data with regard to total protein intake in critically ill children, with only a few studies in the literature in the pediatric burn (46) or surgical (47) populations. Higher protein intakes in critically ill children were recommended based on a higher protein turnover in this population when compared with healthy children whose requirements ranged between 1 and 3.5 g·kg^{-1}·d^{-1} (17, 48). Our patients had an average protein intake of 2.1 g·kg^{-1}·d^{-1} (95% CI: 1.7, 2.4). In addition, it was shown that the amount of protein intake necessary to maintain a nitrogen balance in critically ill patients appears to vary depending on the level of stress, severity of inflammatory response, and the status of organ function (17). Several studies have reported nitrogen balance in critically ill children (19, 26, 27, 49–51). Nitrogen excretion has been shown to be related to the degree of injury and the metabolic state, with urinary urea nitrogen reported as being between 170 and 254 mg·kg^{-1}·d^{-1} in critically ill children (26, 27, 50). In these studies, urinary nitrogen excretion was calculated based on the amount of urea nitrogen in the urine. In the present study the average nitrogen excretion was 347 mg·kg^{-1}·d^{-1}. This could represent differences in measurement techniques. We used the Kjeldahl method to measure total urinary nitrogen because it has been shown that the excretion of urea in critically ill patients is highly variable (52). Another explanation for the higher nitrogen excretion in the present study could be due to differences in the patient population, as assessed by severity of illness scores and the amount of ventilatory support. Verhoeven et al (27) reported mean values for PRISM and TISS scores of 6 and 18, respectively, and a mean inspired oxygen concentration of 0.35. Joosten et al (26) reported a median PRISM score of 7 and a mean inspired oxygen concentration of 0.32. In contrast, the subjects in the present study had average PRISM and TISS scores of 10 (95% CI: 8, 13) and 31 (95% CI: 29, 34), respectively, with an average inspired oxygen concentration of 0.51 (95% CI: 0.48, 0.54). It is important to note that the subjects in the present study received parenteral nutrition as opposed to the 2 reports mentioned above in which patients received mainly enteral nutrition, which implies a less severe disease state. This could be interpreted as supportive evidence that our population was acutely ill, as shown by higher PRISM and TISS scores and inspired oxygen concentration in the ventilator.

Nitrogen balance is a function of both protein and energy intakes. Subjects with a positive nitrogen balance had, on average, a higher ratio of energy intake to energy expenditure (1.7) and a higher protein intake (2.8 mg·kg^{-1}·d^{-1}). These findings support the notion that protein intake partially compensates for increased protein utilization. Adequate amounts of energy are needed to effectively utilize the supplemented protein. From studies of critically ill adults and children it appears that the rates

of protein synthesis are increased when protein and energy are supplied (43, 47, 53–56), but protein breakdown is not affected. Protein turnover is high and protein balance is improved but at the expense of higher protein synthesis. Our results show a higher protein oxidation in subjects with a negative nitrogen balance, with a decrease in protein oxidation at higher intakes, suggesting that the nature of the energy substrate delivered to parenterally fed patients may affect protein metabolism.

In summary, critically ill, mechanically ventilated children receiving parenteral nutrition were hypermetabolic with an average metabolic index of 1.2 and had a negative nitrogen balance of 88 $mg \cdot kg^{-1} \cdot d^{-1}$. Children with a metabolic index >1.1 mainly used fat for oxidation. A higher carbohydrate intake in this population promotes lipogenesis and less oxidation of fat. Negative nitrogen balance was associated with high oxidation rates of protein, implying increased utilization under catabolic conditions. A high protein intake, averaging 2.8 $g \cdot kg^{-1} \cdot d^{-1}$, was associated with a positive nitrogen balance.

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