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Variability of Resting Energy Expenditure in Infants and Young Children with Intestinal Failure-Associated Liver Disease

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Abstract

Objective—To determine, in a cohort of young children with intestinal failure (IF), if estimates of basal metabolic rate (BMR) by standard equations, approximate measured REE by indirect calorimetry (IC).

Methods—IC was performed by dilutional canopy technique. REE measurements were compared to standard, age-based estimation equations (WHO) for BMR. Subjects were classified as hypermetabolic (REE > 110% BMR), hypometabolic (REE < 90% BMR), or normal (REE = 90–110% BMR).

Results—Twenty-eight IF patients (11 female, 17 male) had an underlying diagnosis of necrotizing enterocolitis (n=10) or a congenital gastrointestinal defect (n=18). Median age was 5.3 months. Median (IQR) REE was 46 (42, 58) kcal/kg/day. Median (IQR) total energy intake provided 209 (172, 257)% of REE, with parenteral nutrition providing 76% (23%) of total energy intake. REE was variable, with 39% (n=11) of measurements hypermetabolic, 39% (n=11) hypometabolic, and the remaining 21% (n=6) normal. Although REE was well correlated with estimated BMR ($r = 0.82$, $P < 0.0001$), estimated BMR was not consistently an adequate predictor of REE. BMR over- or under-estimated REE by more than 10 kcal/kg/d in 15/28 (54%) patients.

REE was not significantly correlated with severity of liver disease, nutritional status, total energy intake or gestational age.

Conclusions—Energy expenditure is variable among children with IF and IFALD, with nearly 80% of our cohort exhibiting either hypo- or hypermetabolism. Standard estimation equations frequently do not correctly predict individual REE. Longitudinal studies of energy expenditure and body composition may be needed to guide provision of nutrition regimens.

Introduction

Intestinal failure (IF) in children is defined by dependence on parenteral nutrition (PN) to meet energy, fluid and growth requirements. Residual small bowel length, the health of other organs of digestion and absorption, and other factors generally dictate the degree of malabsorption and consequently the need for specialized enteral or parenteral nutrition.¹ Since its introduction in 1968², PN has become widely accepted as the primary supportive therapy in infants with IF, and mortality due to dehydration and malnutrition has been essentially eliminated.³ This life-saving therapy, however, has been plagued by the recognition that infants with prolonged dependence on PN commonly develop signs and symptoms of hepatic dysfunction. It has also been observed that infants with IF-associated liver disease (IFALD) can have progressive changes in liver histology, including fibrosis and eventually cirrhosis. Several reports have confirmed that the presence of liver disease in patients receiving PN is associated with increased mortality.^{4,5,6}

Multiple risk factors for the development of IF-associated liver disease (IFALD) have been identified, and include premature birth, disruption of the enterohepatic circulation of bile acids, intestinal stasis with subsequent bacterial overgrowth, early and/or recurrent catheter-related sepsis, excessive glucose intake leading to hyper-insulinism and subsequent steatosis, and high parenteral protein, fat and/or energy intake.^{5, 7–10} More recently, the possible role of soybean-based intravenous fat emulsions has been delineated¹¹. Adequate nutrients are essential for optimizing growth and development, but excessive parenteral energy intake could potentiate IFALD. Thus, precise determination of energy requirements might improve clinical and biochemical outcomes.

The energy expenditure of hospitalized children has been examined in several settings, with varying results, even in relatively homogenous patient groups¹². Among children whose resting energy expenditure (REE) was significantly different than that estimated by standardized equations, no clear predictors of hyper-metabolism or hypo-metabolism have emerged^{13–15}. Liver disease has been associated with hypermetabolism in adults¹⁶ and children¹⁷; however, no studies of energy expenditure in children with IFALD have to our knowledge been published. In order to determine whether or not children with IFALD are prone to hypermetabolism, and whether standard equation-based estimates of BMR accurately reflect measured REE, we undertook a prospective evaluation of REE in children with IFALD measured by indirect calorimetry, and compared these results with standard published estimates.

Materials and Methods

Patients with IF underwent measurement of REE as part of our study of ^{13}C -methionine breath test (^{13}C -MBT) to evaluate IFALD. The methodology and description of this study has been previously published¹⁸. Inclusion criteria were 1) a diagnosis of IF (defined as dependence on PN for ≥ 90 days); 2) corrected gestational age ≥ 36 weeks; and 3) the provision of PN to fulfill part or all energy and protein requirements. The diagnosis of IFALD was made by 1) serum direct bilirubin ≥ 2 mg/dL or 2) liver histopathology showing moderate to marked fibrosis in the setting of exposure to PN for ≥ 90 days. Exclusion criteria included 1) receiving parenteral antimicrobials and/or vasopressors; 2) inadequate nutrition support (<80 kcal/kg/d); 3) history of general anesthesia within the previous 48 h; 4) mechanical ventilation; or 5) history of inborn errors of metabolism affecting the methionine metabolic pathway. Children were enrolled from the Center for Advanced Intestinal Rehabilitation (CAIR) at Boston Children's Hospital. After written informed consent was obtained, baseline clinical, anatomic, and biochemical data were collected from the medical record.

On the day of the isotope test, subjects were fasted (no enteral or parenteral nutrition) for 2 hours prior to ^{13}C -methionine administration. Patients were provided intravenous 10% dextrose with normal saline during the fasting period at maintenance fluid rate as determined by the Holliday Segar method. Indirect calorimetry was performed to assess total CO_2 production and O_2 consumption by the dilutional canopy technique (Vmax Encore®, Viasys Healthcare Inc., Yorba Linda, CA). Each indirect calorimetry test was preceded by calibration with a gas mixture of known composition according to the manufacturer's instructions. With the subject in the supine position, a transparent canopy was placed over the head. The indirect calorimeter measures the inspiratory concentration of oxygen (FiO_2) and the difference between FiO_2 and expiratory concentrations of oxygen (FeO_2) using an electrochemical cell, while the expiratory carbon dioxide (FeCO_2) is measured continuously with a non-dispersive infrared thermopile. Inspiratory CO_2 concentration of room air (FiCO_2) is measured every 2 minutes. CO_2 output (VCO_2) and O_2 consumption (VO_2) are calculated each minute and then converted to standard temperature and pressure using dry gas equations. Steady state was defined as a time period of >5 min with $<10\%$ fluctuation in oxygen consumption and carbon dioxide production and $<5\%$ fluctuation in respiratory quotient (RQ). To achieve steady state, each test lasted 20–30 min. The average values of VO_2 , VCO_2 , REE and RQ over the steady state period were recorded.

Measured REE was calculated using the modified Weir equation¹⁹ and expressed as kcal/day. The percentage predicted REE was determined by comparing the REE to the estimated basal metabolic rate (BMR), calculated using the World Health Organization (WHO) estimation equations²⁰. Patients' metabolic states were classified as hypermetabolic if their percent predicted REE (defined as $\text{REE}/\text{BMR} \times 100$) was $>110\%$, hypometabolic if their percent predicted REE was $<90\%$, and normal if their percent predicted REE was between 90 and 110%^{21, 22}.

Body weight was measured by an electronic digital scale accurate to 0.1 kg. Recumbent length was measured by stadiometer to the nearest 0.1 cm. Using the corrected age for

prematurity for infants born at less than 38 weeks gestation, weight for age and length for age z-scores were calculated by the method of Olsen et al²³. Weight for age, length for age, and weight for length z-scores were calculated by World Health Organization growth standards for full-term children less than 2 years of age, and by Centers for Disease Control and Prevention growth references for children 2 years of age or older²⁴. Intake of calories was calculated using published specifications for enteral formulas and parenteral nutrition solutions.

Statistical Analysis

Continuous data are expressed as mean±SD or median (IQR), depending on whether or not the data are normally distributed. The association between continuous measures was evaluated with the Pearson product correlation coefficient. The association of independent variables with the main study outcome was determined by Fisher's exact test, Student's t-test or Wilcoxon rank-sum test. Agreement between REE and BMR was shown using the method of Bland and Altman²⁵. All tests of significance are 2-sided, with statistical significance defined as $P<0.05$.

Results

Baseline subject characteristics are shown in Table 1. Patients ranged in age from 2 weeks to 34 months (median 5.3 months) and were predominantly male (61%). Necrotizing enterocolitis was the most common presenting diagnosis for IF (36%), followed by gastroschisis (25%) and intestinal atresia (25%). Patients were slightly underweight for age, with a mean weight for age Z-score of -1.54 ± 1.51 . Mean±SD weight for height Z-score was -0.84 ± 1.95 . On average, PN was administered for 6 ± 5 months prior to study and comprised $76\pm23\%$ of total calories. Median (IQR) total energy intake was 104 (91, 116) kcal/kg/day. Median (IQR) total energy intake provided 209 (172, 257)% of REE.

Median (IQR) measured REE was 207 (163, 408) kcal/day or 46 (42, 58) kcal/kg/day. Mean (SD) percent predicted REE was $102\pm29\%$, and was correlated with the WHO calculated estimate for age and gender ($r = 0.82$, $P<0.0001$). Compared with estimates of BMR, percent predicted measured REE was variable, with 39% ($n=11$) of measurements consistent with hypermetabolism, 39% ($n=11$) hypometabolism, and the remaining 21% ($n=6$) normal.

Various demographic and clinical factors were explored as possible correlates of metabolic state (Table 2). Neither age, gestational age, weight, stature, Pediatric End-stage Liver Disease (PELD) score, energy intake, % of energy intake from enteral nutrition, length of residual small bowel, nor any available measure of severity of liver disease was associated with metabolic state.

Figure 1a shows the extent of agreement as an absolute difference between REE measured by indirect calorimetry and the WHO estimated BMR by Bland Altman plot. Measured REE tended to be greater than BMR when their mean was > 300 kcal/d, while there was no clear trend below this threshold. On average, the difference between measured REE and BMR was not statistically different from zero, with mean (95% limits of agreement) = -10 (-215 , 195), $P=0.62$. In one case, measured REE was grossly overestimated by BMR and was

beyond the 95% lower limit of agreement. With 28 observations, one is expected to be outside the 95% limits of agreement by chance alone. The non-significant difference between the two methods was unchanged when the outlier point was omitted ($P=0.46$). The wide limits of agreement between the two methods, however, meant that REE was over- or under-estimated by WHO data by more than 10 kcal/kg/d in 15/28 (54%) patients. Figure 1b shows the absolute difference between paired measurements of REE and WHO as a percentage of their mean. This is recommended as a way to stabilize the variation in paired differences, and confirms the interpretation already provided for Figure 1a.

Discussion

Accurate assessment of energy requirements and nutrient delivery by the optimal route are critical elements in the care of children with IF. Energy expenditure is routinely estimated using standard equations and guides nutrient delivery in these patients. We have described, for the first time, measured resting energy expenditure (REE) using indirect calorimetry and the metabolic state in children with IF and IFALD. Although REE was well correlated with estimated BMR ($r = 0.82$, $P < 0.0001$), estimated BMR was not consistently an adequate predictor of REE. BMR over- or under-estimated REE by more than 10 kcal/kg/d in more than one-half of patients. In addition, metabolic state was not predicted by any of the available clinical and nutritional parameters. Reliance on predicted equations therefore may result in suboptimal nutritional prescription with the potential for unintended underfeeding or overfeeding.

Our observations are in accordance with other reports of the inaccuracy of equation estimates of energy expenditure in a variety of patient populations^{13, 26, 27}. Basal energy expenditure calculated using Harris-Benedict and Schofield equations has been shown to be significantly higher than REE obtained by IC in adults with SBS.²⁸ In our current study, the WHO equation underestimated or overestimated the energy expenditure by a wide margin and as a result, patients were at a high risk of unintended underfeeding or overfeeding. Underfeeding in children with IF may result in growth failure. If nutrient intake is guided by BMR, a proportion of patients with hypermetabolism and underestimated energy expenditure may be underfed. Failure to tolerate or absorb enteral nutrients may further add to the inadequacy of energy intake in some patients. Serial weight gain is currently used as the surrogate for optimal nutrition and growth. However, alterations in body composition such as loss of lean body mass from protein and energy underfeeding, and increased fat mass from carbohydrate overfeeding may remain undetected. Future studies examining the role of serial body composition to monitor nutritional status in children with IF are required.

While underfeeding should be avoided, there exists a potential for cumulative overfeeding in a subset of patients with hypometabolism, where equations may overestimate energy expenditure. Total energy intake in our cohort was on average 227% of REE. Malabsorption of enteral nutrients is cited as the reason for prescribing higher energy intakes in children with IF. However, in patients that are fed predominantly by the parenteral route, excess energy delivery could have resulted in a significant risk of cumulative overfeeding in a subset of our cohort. Overfeeding may result in higher carbon dioxide production (VCO_2), respiratory burden, increased fat mass, altered lipid profile and other metabolic

complications. Excessive carbohydrate intake has also been associated with increased lipogenesis and hepatic steatosis, and may be associated with a higher incidence of IFALD or worsening liver function in patients with IF.²⁹

The reasons for the variable metabolic states in our cohort of children with IF and IFALD are not clear. Significant declines in energy expenditure following intestinal resection have been demonstrated in mice, likely as a result of adaptive thermogenesis and reduction in lean body mass³⁰. Whether these changes persist or are similarly present in humans remains an unanswered question. We have previously shown a correlation between lean body mass (LBM) and REE in children undergoing HSCT.³¹ REE was attenuated in this cohort and was highly correlated with LBM measured by dual energy X-ray absorptiometry. Diet composition may also affect REE. High protein energy restricted diet was shown to mitigate the decrease in REE compared to an isocaloric standard protein diet.³² In our current study, we did not observe significant correlations between the metabolic state and variables such as residual bowel length, amount and route of nutrient intake, nutritional status and markers of liver disease.

Several limitations of these data should be noted. Variability of REE compared to BMR may be in part be due to our small sample size, as well as to our inclusion of only children with IFALD. In addition, we did not determine serial REE measures, nor study children whose energy intake was < 80 kcal/k/day. Hence, the true incidence of potential underfeeding or overfeeding cannot be determined. In addition, REE was measured after only a 2 hour fast with supplementary intravenous fluids provided to prevent hypoglycemia. Although conceivably the provision of IV energy may have affected our results, the energy provided was only approximately 3 kcal/kg, and was consistent among all subjects. We therefore suspect that this amount of energy did not contribute to the observed variability in REE measurements.

We have previously reported the risk of overfeeding in children undergoing hemopoietic stem cell transplantation, following cardiac surgery and in those admitted to a multidisciplinary pediatric intensive care unit.^{31, 33, 34} Overall, it is increasingly clear that standard equations fail to accurately estimate the energy expenditure in a wide variety of pediatric patient groups. Most equations incorporate variables such as age, weight, and gender, and are derived from healthy subjects. The wide limits of agreement between the estimated and measured values may result in both underfeeding and overfeeding if energy prescription is based on BMR. Longitudinal studies of energy expenditure and body composition in children with intestinal failure may be needed to guide optimal provision of nutrition.

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Figure 1a.

Bland-Altman plot of the difference between measured REE (MREE) and estimated BMR (WHO), against their mean.

Figure 1b.

Bland-Altman plot of percent difference between measured REE (MREE) and estimated BMR (WHO), against their mean.

Table 1

Baseline characteristics of 28 children with intestinal failure undergoing measurement of resting energy expenditure (REE).

Characteristic	n/N (%), Median (IQR), or Mean±SD
Age (months)	5.3 (3.3, 7.6)
Male sex	17/28 (61%)
Diagnosis	
Necrotizing enterocolitis	10/28 (36%)
Gastroschisis	7/28 (25%)
Intestinal atresia	7/28 (25%)
Others	4/28 (14%)
INR	1.13 (1.06, 1.26)
Weight-for-age Z score	-1.54±1.51
PN intake (kcal/kg/d)	76±20
Total energy intake (kcal/kg/d)	104 (91, 116)
Estimated basal metabolic rate (kcal/day)	244 (177, 329)
Measured Resting Energy Expenditure (kcal/day)	207 (163, 408)
Energy intake/REE × 100	209 (172, 257)
Pediatric End-stage Liver Disease score.	11±6

Table 2

Categorical predictors and unadjusted tests of association with outcome. Shown are n/N (%), mean±SD, or median (IQR).

Characteristic	N	Hyper-metabolic	Hypo- or normal-metabolic	<i>P</i> ¹
Male sex	28	6/11 (54.6%)	5/17 (29.4%)	0.25
History of small bowel resection	19	4/6 (66.7%)	11/13 (84.6%)	0.56
ICV resection	25	2/10 (20.0%)	4/15 (26.7%)	1.00
Presence of diverting intestinal stoma	27	5/11 (45.5%)	4/16 (25.0%)	0.41
Corrected age (wks)	28	15.7 (3.5, 25.3)	12.4 (7.4, 22.9)	0.71
Gestational age (wks)	28	33.0 (26.0, 35.6)	32.0 (29.0, 35.5)	0.93
Weight-for-age z-score	28	-1.99±1.42	-1.25±1.53	0.21
Height-for-age z-score	28	-1.44±1.17	-1.26±1.66	0.76
Weight-for-height z-score	28	-1.58±1.38	-0.43±2.13	0.16
PELD	26	9.0 (6.0, 19.0)	12.0 (9.0, 15.0)	0.84
INR	26	1.25 (1.11, 1.37)	1.10 (1.05, 1.23)	0.08
Residual small bowel (cm)	17	42.5 (25.0, 45.0)	27.0 (14.0, 40.0)	0.29
Months on PN	27	7.0 (3.0, 7.0)	4.0 (3.0, 7.0)	0.82
Total energy intake (kcal/kg/d)	28	104.0 (94.0, 116.0)	93.0 (90.0, 117.0)	0.61
% energy intake from EN	28	10.3 (4.4, 30.3)	17.4 (8.6, 47.7)	0.68
Energy intake/REE × 100	28	176.3 (129.7, 206.3)	226.8 (205.6, 297.3)	0.25
Respiratory quotient	28	0.95 (0.89, 0.99)	0.94 (0.90, 1.00)	0.78
¹³ C-MBT % recovery at 120 minutes	27	7.8 (4.8, 11.9)	6.0 (3.1, 7.9)	0.24
Liver histology ²	14	2.0 (1.0, 3.0)	2.0 (2.0, 3.0)	0.34

¹ *P*-value from Fisher exact test, Student's t-test or Wilcoxon rank-sum test.

² Histology scale: 1=inflammation, 2=fibrosis, 3=cirrhosis. Comparison restricted to 14 subjects with liver biopsy.