Resting energy expenditure in disorders of propionate metabolism

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Objectives: During intercurrent illness children with methylmalonic acidemia were found to have increased resting energy expenditure (REE). We measured REE in children with disorders of propionate metabolism (methylmalonic and propionic acidemia) when they were well and compared the values with those predicted by the Schofield equation.

Study design: Prospective study in tertiary care facility. REE was measured with open-circuit indirect calorimetry under standardized conditions. Predicted REE values were calculated with the Schofield equation. Fourteen subjects with propionic acidemia (n = 3) and methylmalonic acidemia (n = 11) were studied.

Results: The median REE was 690 kcal/d (range 186 to 1687 kcal/d), which is significantly reduced, representing 80% ± 18% of that predicted by the Schofield height and weight equation ($P < .01$). REE was significantly lower in female compared with male patients for unknown reasons. There were no differences with age or neurologic state. REE was not further reduced in those with chronic renal failure.

Conclusion: REE in patients with disorders of propionate metabolism is reduced when they are well. (J Pediatr 2000;136:659-63)

Diet is the mainstay of treatment in disorders of propionate metabolism, methylmalonic, and propionic acidemia. However, little is known about actual energy requirements in these conditions. Intakes of energy and protein are based mainly on current recommendations for healthy children.[1-4] The recommendations for energy intake during acute illness are empirical.[5] Many factors contribute to resting energy expenditure in children.[6] In a recent preliminary study, we showed that REE was increased by up to 30% in 2 children with MMA during intercurrent illness.[7] For clinical and ethical reasons, it has not been possible to study additional subjects with MMA during intercurrent illness.

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Equations to predict REE are used frequently for clinical management. The Schofield equation with weight and height[8] and the FAO/WHO/UNU[2] equations have been found to predict REE most accurately in children.[9] The Harris-Benedict equation is known not to be accurate in infancy and in states of malnutrition.[10,11] Indirect calorimetry is widely used to measure REE in healthy children and in various diseases.[11-16] We have used this technique to measure REE in patients with MMA and PA when well and have compared the observed results with the REE predicted by the Schofield equations.

BMI	Body mass index
MMA	Methylmalonic acidemia
PA	Propionic acidemia
REE	Resting energy expenditure

Subjects and Methods

Fourteen patients (MMA [$n = 11$] or PA [$n = 3$]) 6 weeks to 16 years old (median 9 years) were studied when well (Table I). Five of those with MMA presented in the neonatal period and 6 later in childhood, as did all patients with PA.

Informed written consent was obtained from parents, and when appropriate the patient's consent was also obtained. All the children were admitted to the day care unit for the study.

Weight was measured with a digital electronic stand-on scale or an infant scale (precision to 0.1 and 0.01, kg respectively). Height was measured to

Table I. Clinical details of patients with propionic and methylmalonic acidemia

Patient	Age	Sex	Disease	Mvmt D	Dev del	Cer Atr	CRF	Ptintk
1	0.12	F	NMMA	–	+	+	–	2.1
2	0.32	F	NMMA	–	–	–	–	ND
3	1.7	M	LMMA	++	+++	+++	–	1.4
4	2.02	F	NMMA	+++	+++	++	–	2.0
5	7.05	M	LPA	–	+	–	–	ND
6	7.23	F	LMMA	–	++	–	–	1.5
7	8.64	M	LPA	+++	++	–	–	1.2
8	8.95	F	LMMA	–	+	–	–	1.1
9	11.76	F	LMMA	++	+	+	+	0.9
10	12.05	F	LMMA	–	–	–	–	ND
11	12.32	M	NMMA	+	–	–	+	0.9
12	12.43	M	NMMA	++	++	+	+	1.0
13	15.59	M	LMMA	–	+	–	HD	0.6
14	16.05	F	LPA	+	–	–	–	0.9

NMMA, Neonatal onset methylmalonic acidemia; *LMMA*, late onset methylmalonic acidemia; *LPA*, late onset propionic acidemia. Neurologic findings: – absent, + minor, ++ moderate, +++ severe. *Mvmt D*, Movement disorders; *Dev Del*, developmental delay; *Cer Atr*, cerebral atrophy. Renal disease: *CRF*, chronic renal failure (creatinine clearance <50 mL/min/1.73 m^2); *HD*, patient receiving hemodialysis; *Ptink*, protein intake (g/kg/d); *ND*, not determined.

Table II. Schofield, weight, and height equation (MJ/day) (1 kcal = 4.186 kJ)

Children <3 years of age
Boys: REE = 0.07 × Weight (kg) + 6.349 × Height (cm) – 2.584
Girls: REE = 0.068 × Weight (kg) + 4.281 × Height (cm) – 1.730
Children 3-10 years of age
Boys: REE = 0.082 × Weight (kg) + 0.545 × Height (cm) + 1.736
Girls: REE = 0.071 × Weight (kg) + 0.677 × Height (cm) + 1.553
Children 10-18 years of age
Boys: REE = 0.068 × Weight (kg) + 0.574 × Height (cm) + 2.157
Girls: REE = 0.035 × Weight (kg) + 1.948 × Height (cm) + 0.837

0.1 cm with a stadiometer or an infant length board. Skinfolds were measured with a skinfold caliper (Holtain) on the nondominant side. Mid-arm circumference was measured on the same arm. Weight and height percentiles were calculated from British growth standards.[17] The body mass index was calculated as weight/height^2 and was expressed in kilograms per meter squared.[18] The upper arm muscle area, which can be used to predict the muscle protein mass, was calculated in 9 patients with the Frisancho equation and compared with the normal values for upper arm muscle area.[19]

REE was measured by open circuit indirect calorimetry (Deltatrac metabolic monitor, Datex Instrumentarium Corp, Helsinki, Finland) as previously reported.[7] Age, sex, weight, height, and an age-adjusted value for urinary nitrogen[20] were entered before each measurement was made. Values for urinary nitrogen were taken from a study in healthy children.[20] The use of these values for our study population may have introduced a small but insignificant error depending on the differences in dietary protein intake. None of the subjects studied received additional amino acid supplements. The instrument was calibrated before each measurement with calibration gas (CO_2 5%, O_2 95%, Datex) and periodically by ethanol combustion.

REE is typically measured in the resting fasting subject, but it was not possible to fast most of the patients overnight (>12 hours) because of the risk of metabolic decompensation. For most of the patients (n = 10) the fasting period was 8 hours, but the youngest children (n = 4) could not even fast for this long, and consequently their respiratory quotient was >0.9. In these subjects the REE was reduced by 10% to account for any thermogenic effect of the diet.[21]

Children rested on a bed for approximately 20 minutes before REE was measured with the canopy. The first 5-minute period was not included, and measurements were accepted only when a steady state was achieved. All measurements took place in a quiet thermoneutral environment as previously described.[7] For comparison, predicted REE was calculated with the Schofield equation adjusted for age and sex with weight and height[8] (Table II).

Data Analysis

Age in years, weight and height in percentiles, protein intake in grams per kilogram per day, and REE in kilocalories per day are expressed in median

Table III. Anthropometry

	No.	Age (y)	Weight percentile	Height percentile	BMI z scores
All patients	14	8.95 (0.12-16)	40 (3-97)	25 (3-97)	0.10 ± 1.10
Male	6	7.6 (0.12-15.6)	45 (25-97)	25 (7-97)	0.45 ± 0.40
Female	8	10 (0.32-16)	40 (3-90)	25 (3-80)	−0.17 ± 1.37
Neonatal onset	5	2 (0.12-12.4)	50 (3-55)	40 (3-75)	−0.82 ± 0.81*
Late onset	9	8.9 (1.7-16)	40 (10-97)	20 (3-97)	0.60 ± 0.91*

Age, weight, and height are expressed in median and range. BMI z scores are expressed in mean ± SD. Unpaired t test was used to test for differences within the 2 subgroups (sex and age at presentation).
*$P < .01$.

and range. The percentage of predicted values of REE is expressed as mean ± SD. BMI z scores were calculated with the data of Cole et al.[18]

Statistics were calculated with Statview SE + graphics (Abacus Concepts, Inc, Berkeley, Calif) with an unpaired t test to analyze differences between the groups.

Two methods, similar to those used by Kaplan et al,[9] were used to determine whether measured REE was consistently and significantly different from predicted REE. With method 1 a paired t test was used to test for differences between the measured and the predicted REE. With method 2 the percentage of predicted REE by the Schofield equation was calculated as measured REE divided by predicted REE, which allows for comparisons across the wide range of age, weight, sex, and onset of disease.

Correlations between variables were determined with simple regression analysis.

A P value of .05 or less was considered to be statistically significant.

RESULTS

Anthropometric data of our study population divided into subgroups are summarized in Table III. Weight (z score −0.44) and height (z score −0.95) were lower compared with the U.K. growth standards. There was no trend with age. A significant difference was seen in BMI z scores between late onset and neonatal onset groups ($P < .01$).

Table IV. Resting energy expenditure compared with predicted values

	No.	REE (kcal/d)	Predicted (kcal/d)	%
All patients	14	690 (186-1687)	1112 (141-1689)*	80 ± 18
Male	6	805 (186-1687)	1118 (141-1689)	88 ± 18
Female	8	646 (290-1244)	1099 (360-1331)*	75 ± 16
Neonatal	5	576 (186-1136)	555 (141-1480)	90 ± 29
Late onset	9	761 (557-1687)	1128 (582-1689)*	78 ± 15

Measured and predicted resting energy expenditure (REE) are expressed as median and range; % represents measured REE as percentage of the predicted value. Paired t test was used to examine the difference between measured and predicted REE values. Unpaired t test was used within subgroups (age, sex, and age at presentation) with percentage data.
*$P < .01$.

In 9 patients (8 >3 years old) the upper arm muscle area was 2541 ± 961 mm^2 (99.1% ± 11% of the reference values),[13] indicating normal muscle protein reserves. The subjects were receiving low protein diets (median 1.10 g protein/kg/d [range 0.6 to 2.1]) (Table II). None of the subjects studied received additional amino acid supplements. Energy intakes are calculated to provide the normal requirement for age.[1]

To test the accuracy of our method, REE was measured in 6 healthy children (4 male, 2 female, age range 20 months to 12 years) after an overnight fast. There was good agreement between measured REE (mean 1060, range 700 to 1710 kcal/d) and predicted REE (1001, 700 to 1470 kcal/d).

A close correlation was seen between measured and predicted REE ($r = 0.9$, $P < .01$), although the overall REE was lower in our study population compared with predicted values (Table IV). Within subgroups (age, sex, or time of onset of disease) no correlation was seen between REE and daily protein intake or with neurologic status.

Four patients in chronic renal failure including one who was receiving hemodialysis had a normal REE.

DISCUSSION

With indirect calorimetry we measured REE in 14 patients with MMA and PA. Overall, REE was reduced by 20% compared with the Schofield equation, which has previously been shown to predict REE in both healthy and ill children.[9,12-16]

The reduction of REE could be due to several factors, which distinguish this group of children from their healthy peers. First, the patients are treated with a low protein diet varying from 0.39 to 1.58 g/kg/d. This intake is

similar to the protein intake reported at 0.75 and 1.10 g/kg/d in 2 patients with MMA by Ney et al[22] and is in accordance with the latest published recommendations for safe levels of protein intake in childhood.[1-4] Previous work has shown that REE in patients in chronic renal failure or with phenylketonuria on low protein diets of 0.55 to 0.6 g/kg/d was not altered.[23,24]

Second, between 20% and 30% of REE is related to muscle mass in adults,[25] but muscle mass in children is relatively lower. Nonobese boys with Duchenne muscular dystrophy[26] who have a marked reduction in lean body mass (loss of 71% of muscle mass) have a 13% reduction in REE, which is close to that predicted.[26] To exclude any effect of body composition, we have measured the upper arm muscle area in 9 children. This is related to the reserves in muscle protein and was normal compared with previously published data.[19]

Third, 4 of the children with MMA have chronic renal failure, and one is treated currently with hemodialysis. Monteon et al[23] found that in patients with chronic renal failure, REE was 91% of that of a control group without hemodialysis and 97% of that of a control group when these patients were treated with hemodialysis. In our patients we failed to demonstrate any relationship between renal disease and REE. We have one patient (studied twice) with MMA who is treated with hemodialysis, and he has a normal REE.

Fourth, neurologic status can have a major effect on REE. In children with quadriplegic cerebral palsy, the reduction of REE is poorly correlated with body cell mass, and it is postulated that the central nervous system is an important regulator of basal energy metabolism in children.[27] The neurologic outcome of children with MMA and PA is often poor, because movement disorders, developmental delay, and cerebral atrophy are common.[28,29] In our study group, only 2 children were normal with no neurologic involvement, 1 infant 4 months old and 1 with vitamin B12-responsive MMA, both with REE close to predicted. Thus neurologic impairment may have contributed to the reduced REE.

The difference between REE in female and male patients is difficult to explain. First, it could be a chance finding. Second, there are differences in those 2 groups with respect to growth and BMI. Third, there are differences in severity and onset of disease. In summary, we believe that the differences in REE between the 2 groups are most likely caused by a combination of several factors.

Mitochondrial impairment could play a major role in children with MMA both when well and unwell, because accumulation of methylmalonic acid interferes with mitochondrial function.[30] In the well state this accumulation may reduce substrate flux, whereas in the unwell state a threshold may be exceeded that uncouples the respiratory chain.[30] For these children, when they are well, normal energy intake is sufficient for growth, particularly in light of reduced REE levels. However, when these patients become unwell, their REE may rise,[7] and the energy intake should be increased to take account of this and to prevent possible metabolic decompensation.

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