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Assessment of energy expenditure in metabolic disorders

Abstract The assessment of energy expenditure is valuable for the management of children with various conditions such as obesity and failure to thrive. Total daily energy expenditure (TDEE) includes resting energy expenditure (REE), energy expenditure during physical activity, dietary thermogenesis and growth. TDEE can be assessed by using the double-labelled water technique, but it has complex pitfalls and potential sources of errors and is impractical for everyday use. As REE is a substantial part of TDEE (65%–70%) and computerised indirect calorimeters have become recently available, this non-invasive, relatively cheap and easy to use technique is valuable for the assessment of short-term changes in energy metabolism. This can be used to assess REE of children with inborn errors of metabolism, whilst well and during episodes of metabolic decompensation and therefore to accurately determine energy intake.

Key words Metabolic decompensation · Double-labelled water · Resting energy expenditure · Preterm infant · Methylmalonic acidaemia

Abbreviations *FTT* failure to thrive · *REE* resting energy expenditure · *TDEE* total daily energy expenditure · VCO_2 carbon dioxide production · VO_2 oxygen consumption

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Introduction

The assessment of energy expenditure and daily energy requirements is crucial for diagnosis and management in children with obesity and failure to thrive (FTT), as well as for many other conditions, in which changes in energy metabolism might play an important role in the pathophysiology of the disease. Such information is potentially valuable in children with inborn errors of metabolism, but information is very limited, despite problems with growth and metabolic decompensation [3, 14].

Total daily energy expenditure (TDEE) includes resting energy expenditure (REE), diet induced thermogenesis, physical activity and growth (Fig. 1) [14]. TDEE can be measured by the double labelled water technique (^2H_2O and $H_2{}^{18}O$) [15, 18], cumulative heart rate monitoring [11] or whole room calorimetry [16]. These are all complex and time consuming. The measurement of REE has recently become easier with the development of computerised monitors [14, 17]. As the major component of TDEE, the measurement of REE is valuable for monitoring changes in energy metabolism [14].

In this review we will describe the two primary techniques for studying energy metabolism – indirect calorimetry and double labelled water technique and present results of some of our studies.

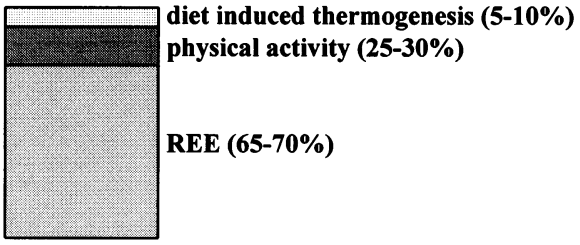

Fig. 1 Total daily energy expenditure in children

Indirect calorimetry

Indirect calorimetry has been developed in the 1920s for studies of energy metabolism in animals [13] and since then been modified and improved extensively [6, 14]. It has been the subject of several major reviews and scientific reports [1, 4, 5–7, 9, 10, 12].

Indirect calorimetry estimates the metabolic rate from measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Additional information on substrate utilisation (i.e. lipolysis and glucose oxidation) can be obtained by calculation [5, 6, 14]. The essential assumption is that under steady state conditions respiratory gas exchange is in equilibrium with gas exchange within the mitochondria, thus measuring indirectly oxidative phosphorylation [6].

Since the introduction of commercially availabe computerised indirect calorimeters (f.ex. Deltatrac and Deltatrac II) indirect calorimetry has become technically simpler and can be used clinically for studying energy and substrate metabolism. In addition it is used for the measurement of VCO_2 for studies using stable isotope tracer in both children and adults to measure substrate oxidation rates [7].

Indirect calorimetry can be used either in the open circuit or closed circuit mode, on spontaneously breathing or mechanically ventilated patients respectively. The flow rate can be adjusted to values from 3 l/min up to 80 l/min, allowing measurements on preterm newborn with 1 kg up to subjects with 120 kg body weight and more. The measurement of REE in mechanically ventilated, critically ill children is of particular interest for the management of these children, assessing energy requirements and substrate utilisation [2]. However, the indirect calorimeter cannot be used on constant flow ventilators due to the positive flow during the expiratory phase, resulting in sampling errors within the indirect calorimeter.

Spontaneously breathing subjects are studied under controlled, reproducible conditions following a defined protocol (Table 1). However some adjustments have to be made for measurements in preterm infants, younger children and children with movement disorders, who are active and not resting, because they are not in a steady state. Measurements should only be started when the child has settled and is not crying. To reduce the problems younger children are usually kept under the hood by allowing them to watch videos or by reading books to them. Activity scores can be used in preterm infants to correct the measured REE [8]. However it can be argued that children who are unsettled never achieve steady state conditions and therefore measurements might overestimate the true REE [14].

Table 1 Protocol for studies using indirect calorimetry – own experience –

1. Overnight fast or where not possible after 3–4 h of fasting (postabsorptive state)
2. Thermoneutral, non-stimulating environment
3. Subject rest at least 15 minutes prior to measurement on bed
4. Measurement for 45–60 minutes (up to 4–6 h in preterm infants)
5. Closed eyes, not asleep (activity score)
6. Gas calibration before each measurement
7. Alcohol burning test once a month (or each 30 measurements)
8. Cleaning of equipment (hood, adaptors) after each measurement

Double-labelled water method

The general principle of this method is based on the assumption that ingested double-labelled water (^2H_2O and $H_2{}^{18}O$) is distributed rapidly and homogeneously within the body water pool and more importantly that oxygen atoms in exhaled carbon dioxide and water are in isotopic equilibrium. This is due to the enzyme carbonic anhydrase, which maintains equilibrium between CO_2, H_2O and carbonic acid [15, 18]. By giving a dose of $H_2{}^{18}O$, both the water and carbon dioxide pool will be labelled, whereas when ^2H_2O is given only the water pool will be labelled. The difference between the elimination rates of $H_2{}^{18}O$ and ^2H_2O is therefore a function of VCO_2, which is proportional to TDEE (Fig. 2) [15, 18].

Several additional assumptions have to be made and corrections applied. There is significant isotopic exchange between deuterium and N-H, S-H and C-H groups occurring within days, which leads to false low enrichment in ^2H_2O and overestimation of ^2H_2O elimination rates. Total body water, water flux and VCO_2 should remain approximately constant throughout the sample period (5–14 days). This is difficult to achieve in critically ill, mechanically ventilated subjects with infusions and/or fluid overload or restriction and in preterm infants in incubators. The diet and its isotopic enrichment has to be kept constant throughout the study period to ensure no changes in background enrichment [15, 18].

This technique has many potential pitfalls and the underlying mathematical model is complex. Thus the technique does need to be adapted to the individual needs of the investigator, prior to any study. The protocol we have

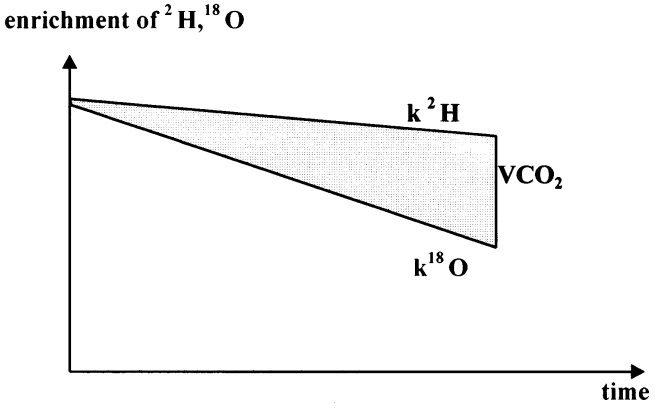

Fig. 2 Principle of double-labelled water technique (k^2H: elimination rate of ^2H, $k^{18}O$: elimination rate of ^{18}O)

Table 2 Recommended protocol for double-labelled water method in preterm infants

1. Sample urine or blood for background enrichment
2. Weigh infants accurately daily
3. Administer isotopes (doses range from 0.25 g/kg to 1 g/kg for either isotope)
4. Precisely timed sample every 12–24 hours (urine or blood)
5. Transfer samples to deep freezer (–70° C) until analysis

used for our studies in preterm infants is shown in Table 2. The equations for preterm infants and older children and adults for the calculation of total body water and TDEE have been described in detail elsewhere [15, 18].

Studies in preterm infants

We studied energy metabolism in a group of spontaneously breathing, clinically stable preterm infants by using the double-labelled water technique and indirect calorimetry simultaneously together with nitrogen excretion (unpublished data). The double-labelled water technique has been used as described above and urine samples collected daily up to 12 days. Indirect calorimetry has been done continuously for 24 h, including the measurement of dietary thermogenesis and activity, thus reflecting TDEE rather than REE. The results in eight preterm infants are shown in Table 3. VCO_2 can be determined reliably by using either method, but indirect calorimetry should be preferred because the results are obtainable within 24 h and the method is relatively cheap compared to the high costs of $^2H_2{}^{18}O$.

Studies in Duchenne muscular dystrophy

However indirect calorimetry can lead to false conclusions when used in subjects whose respiratory gas exchange is impaired. In subjects with Duchenne muscular dystrophy we found recently an apparent increase in REE with age when compared to healthy controls (Fig. 3). This could be explained by the fact that expiratory CO_2 concentrations increase by time in these patients due to increased periods of nocturnal hypoventilation (Fig. 4).

Table 3 VCO_2 in preterm infants – comparison of double-labelled water technique and indirect calorimetry over 24 h

Subject	Mass (g) before	Mass (g) after	VCO_2 ($^2H_2{}^{18}O$) (ml/kg/min)	VCO_2 (calorim.) (ml/kg/min)
1	1000	1160	8.06	8.01
2	1110	1200	7.50	6.88
3	1320	1600	9.03	8.25
4	1520	1760	6.67	7.38
5	1360	1610	8.12	7.04
6	1210	1490	7.29	7.16
7	870	1060	7.22	8.11
8	1070	1250	6.51	–
Mean	1183	1391	7.55	7.55
SD ±	211.8	255.4	0.829	0.563

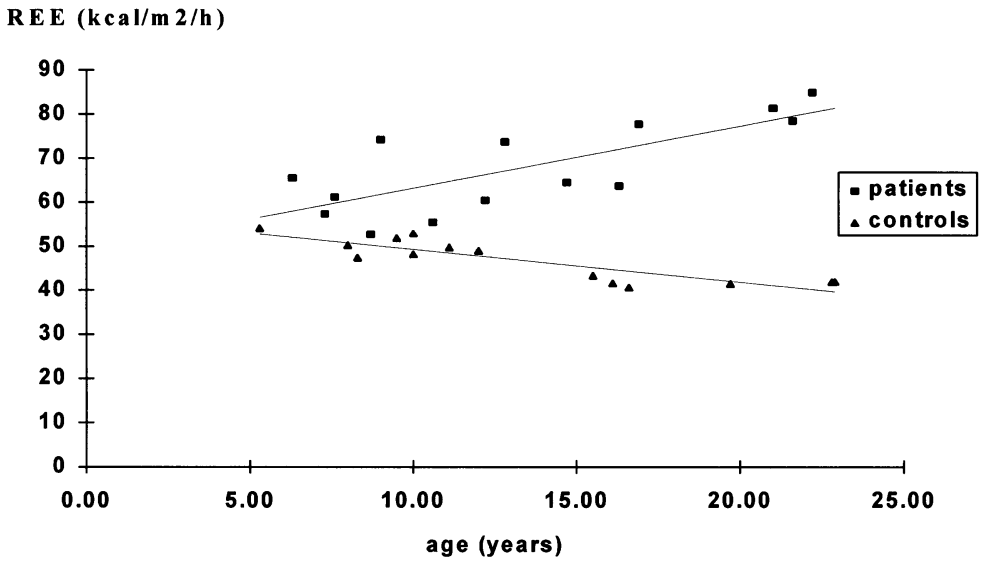

Fig. 3 REE in subjects with Duchenne muscular dystrophy and controls

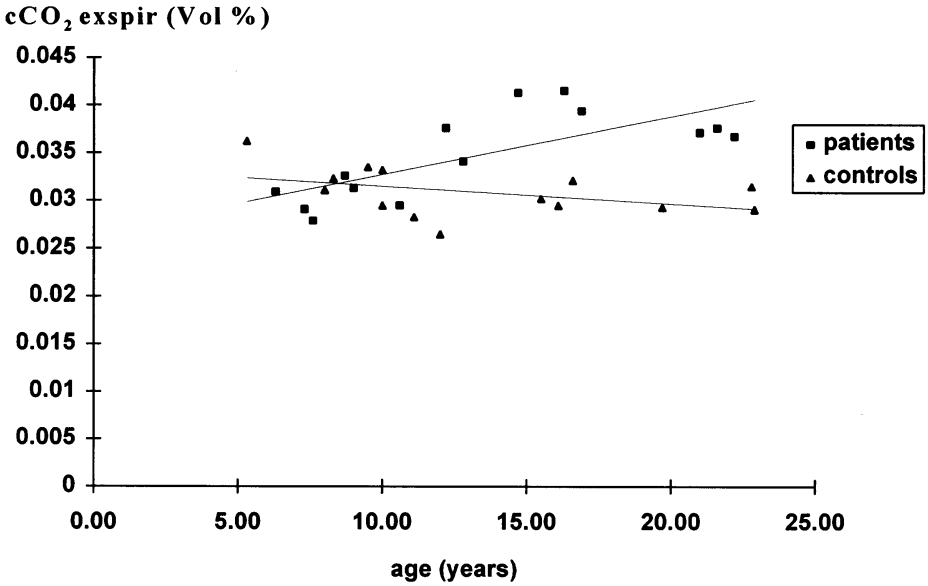

Fig. 4 Expiratory CO_2 concentrations (cCO_2) in subjects with Duchenne muscular dystrophy and controls in relation to age

Table 4 Indirect calorimetry in inborn errors of metabolism (*MMA* methylmalonic acidaemia, *RQ* respiratory quotient)

Disease	Age	Weight	REE	RQ	REE/kg
Stable MMA	3 months 3 weeks	6.1 kg	290 kcal/day	0.92	49.2/kg
Stable MMA	1 year 8 months	11 kg	570 kcal/day	0.90	51.8 kg
Decomp. MMA	11 months 2 weeks	5.7 kg	405 kcal/day	0.90	72.8/kg
Decomp. MMA	2 years	8 kg	570 kcal/day	0.83	71.2/kg
Controls (ref)	1 day – 4 months	0.92–5.2 kg	N/A	N/A	49.6 ± 0.70/kg

Studies in inborn errors of metabolism

There is very little information on energy metabolism in inborn errors of metabolism, despite its value in management of episodes of metabolic decompensation. We have performed preliminary studies of REE and substrate utilisation in children with methylmalonic acidaemia, when well and during metabolic decompensation. REE increased at least 30%–40% during decompensation, which underlines the importance of a high energy intake (Table 4).

Conclusions

Energy expenditure can be measured using both double-labelled water and indirect calorimetry. These techniques provide important insights into the energy requirement under different conditions. Extended studies will provide guidelines for future management of metabolic patients during metabolic crisis and possibly measures to optimize the nutritional regimen individually.

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