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ORIGINAL ARTICLE

Total energy expenditure in stable patients with cystic fibrosis

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Abstract—Background and aims: Undernutrition is a common problem in patients with cystic fibrosis and is associated with a poor prognosis. The two aims of this study were to assess and compare the two main field techniques in the measurement of total energy expenditure and, secondly, to assess total energy expenditure in stable patients and compare with healthy controls.

Methods: Resting energy expenditure was measured using indirect calorimetry and total energy expenditure was measured using 24-h heart rate (HR) methodology and doubly isotopically labelled water.

Results: Seventeen patients, mean age 23 years and FEV₁ 52% predicted and thirteen controls were recruited. Resting energy expenditure was higher in patients 0.24 (0.03) MJ/kg Fat-Free Mass (FFM) compared to controls 0.22 (0.02) MJ/kg FFM, $P=0.02$. Twenty-four hour heart rate underestimated total energy expenditure, 9.49 (1.85) MJ/day in patients compared to 11.69 (2.79) MJ/day using doubly labelled water. There was no difference in total energy expenditure in patients and controls using both methods, 11.69 (2.79) MJ/day compared to 11.38 (2.71) MJ/day using doubly isotopically labelled water.

Conclusions: In clinically stable young adult patients with moderately severe respiratory disease total energy expenditure is comparable to that in a control population despite an increase in resting energy expenditure and both 24-h HR and doubly isotopically labelled water are suitable for use in patients with cystic fibrosis. © 2001 Harcourt Publishers Ltd.

Key words: cystic fibrosis; energy expenditure

Introduction

Survival for patients with cystic fibrosis (CF) has improved since the condition was first described in 1938, when it was usually a post-mortem diagnosis in affected babies (1). It is estimated now that the median survival for children in the UK born in the 1990s is 40 years (2). This improved survival has been attributed to a number of factors including early diagnosis, aggressive physiotherapy, potent antibiotic therapy and the development of CF centres (3, 4). Nutritional status has also been identified as an important prognostic factor (5, 6).

Undernutrition, however, remains a problem in many patients with CF. Recent studies have shown that patients with CF still have height and weight indices below the mean for the population (7–9). This implies an imbalance between energy intake and total energy expenditure (TEE), but the causes of this imbalance in CF are unclear. TEE is composed of resting energy expenditure (REE), dietary induced thermogenesis and physical activity. REE, which comprises about 70% of TEE is elevated in CF, but very little is known about

TEE in patients. The only previous study to measure TEE in adolescents found that it was similar in a stable population of patients with CF to an age and sex matched control group. TEE was measured by 24-h heart rate (HR) methodology (24-h HR) (10). Other studies have measured TEE in infants and children with CF. Shepherd et al. assessed TEE in clinically stable infants with CF using doubly labelled water (DLW) and found that in infants with CF, TEE was increased compared to a control population (11). Tomezsko et al. measured TEE in pre-pubertal children using DLW and found TEE to be increased in those children who were $\Delta F508$ homozygotes compared to a control population (12). However, other studies have found that TEE in infants and pre-pubertal children with CF is not different compared to control populations (13). These conflicting results may reflect a difference due to the markedly different ages of the populations studied or it may reflect a methodological problem as different field techniques were used in these various studies.

In this study TEE was measured in a group of stable young adults with CF using two independent techniques. DLW and 24-h HR are the most commonly used field techniques for the measurement of TEE, however, although both techniques have been extensively validated in normal populations, there are no studies

comparing the two techniques in patients with CF (14–17). The aim of this study was to assess repeatability of 24-h HR methodology for use in patients with CF and compare DLW and 24-h HR in the assessment of TEE in a stable population of young adult patients with CF.

Methods

Seventeen patients with CF who were clinically stable and 13 age, sex and weight matched controls were studied. The study period was 2 weeks. Patients with moderately severe lung disease, $30\% < FEV_1 < 70\%$ were invited to participate in the study and were considered to be clinically stable if their FEV_1 was within 5% of their best over the previous 6 months, they were not on antibiotics and had no symptoms suggestive of an exacerbation of respiratory symptoms. All patients were taking pancreatic enzyme supplements, oral vitamin supplements and some took inhaled bronchodilator therapy. Controls were on no medication and had no intercurrent illnesses. The study was approved by the local ethics committee.

On the first day of the study subjects came to the investigation room between 08:00 and 09:30 having fasted from midnight. Patients had taken their morning medication apart from nebulized or inhaled beta agonists.

REE and TEE (24-h HR) measurements

REE was measured by open circuit indirect calorimetry using a Quinton Qplex machine with a face mask. A preliminary study had been undertaken to compare REE measurements using both a face mask and mouth piece with the Quinton Qplex. There was no difference in REE measurements using both methods, but patients and controls preferred the face mask as it was more comfortable. A face mask was therefore used in all subjects for the measurement of gas exchange. After an acclimatization period of 20 min, gas exchange measurements were recorded each minute for a further 20 min. All subjects had visited the investigation room on one previous occasion when they had been familiarized with the equipment. Subjects then had a rest period of 30 min. Individual heart rate oxygen consumption curves were then calibrated for each subject as described previously (16–19). Subjects sat for 6 min, stood for 6 min and walked on a treadmill at two different work loads for 6 min each. Most patients and all of the controls walked at a speed of 2.7 km/h and a gradient of 5% followed by a speed of 4 km/h and a gradient of 10%. Patients not able to exercise at these limits had been identified at the initial familiarization visit. These patients walked for 6 min at 2 km/h at a zero gradient followed by 2.7 km/h at a zero gradient. After an initial calibration period readings of heart rate and gas

exchange were recorded each minute for the last 3 min of each period. After the exercise period heart rate monitors (Polar Sports Tester, Kempele, Finland) were then attached to the subjects with instructions to take them off as they were going to bed to sleep that night.

TEE (DLW) measurements

Subjects were then given a previously weighted dose of DLW which contained 0.15 g/kg body water 2H_2O and 0.30 g/kg body water H_2O^{18} . The Maastricht protocol for the measurement of TEE using DLW was used in this study (20) and subjects were instructed to drink the contents at 22:00 on day zero and after overnight equilibration, collect urine samples on days one, eight and fifteen, the second voiding of the morning and the last voiding at night in all cases. Subjects returned to the examination room between day eight and day 14 and had their REE measured again and underwent repeat calibration for heart rate oxygen consumption curves. Subjects wore the heart rate monitor as on day zero. All urine samples were recovered by the examiner the day after collection.

Fat-free mass (FFM) was estimated from the first urine sample on day one as described previously (20). REE was calculated using the equation of Elia and Livesey (21). Total energy expenditure was calculated from the rate of disappearance of this isotopes as described previously (20, 22). Data from the heart rate monitors was converted into oxygen consumption and indirectly energy expenditure from each persons calibration curves.

Statistical analysis

Statistical analysis of repeatability of measurements of TEE using 24-h HR methodology was by the method of Bland and Altman (23). Comparison between patients and controls was by non-parametric Mann–Whitney U-testing. Agreement between the two methods for assessing TEE was assessed by the method of Bland and Altman. REE measurements were expressed in MJ/kg FFM and % predicted according to the equations of Schofield (24). TEE was expressed in MJ/day.

Ethical approval

This study was approved by the ethical committee of Queens University of Belfast and all subjects gave written, informed consent to participating in the study.

Results

The patients with CF had lower weight, BMI and lung function compared to controls. The mean % predicted

FEV₁ of the CF population was 52 (12)%. The percent FFM was significantly higher in the CF study group compared to the control population, 59.2 (11.2)% and 55.5 (5.8)%, $P=0.04$ (Table 1).

Resting energy expenditure was higher in patients, 0.24 (0.03) MJ/Kg FFM compared to controls, 0.22 (0.02) MJ/kg FFM, $P=0.02$. When REE was expressed as % predicted from the equations of Schofield, mean % predicted REE in patients was 127.4 (14.1)% compared to 113.4 (12.3)% in controls, $P=0.04$. The coefficients of variation for repeated measurements of REE were 7.9% in patients and 12.6% in controls.

There was no statistical difference in TEE in patients and controls using 24-h HR methodology, 9.49 (1.85) MJ/day in patients and 9.84 (2.07) MJ/day in controls, (Table 2). When TEE measurements were expressed per kg of body weight and per kg of FFM there was still no difference between patients and controls. All subjects

kept the HR monitors on during their waking hours from about 11:00 until going to bed. All subjects had at least 2 separate days when they wore the HR monitor and six patients and five controls had 3 days. The error standard deviation for repeated measurements of TEE using 24-h HR methodology was 0.02 MJ/kg/day in patients and 0.02 MJ/kg/day in controls giving coefficients of variation of 10% in patients and 10.5% in controls.

Eleven patients and 10 controls had TEE measured by DLW in addition to 24-h HR methodology. There was no significant difference in TEE between patients and controls using DLW methodology, 11.69 (2.79) MJ/day in patients compared to 11.38 (2.71) MJ/day in controls. When TEE was expressed as MJ per kg FFM controls had a higher energy expenditure, $P<0.05$ (Table 2). TEE values by DLW were higher than 24-h HR values, mean % difference in patients being 8.8 (7.9)% and in controls mean % difference between the two methods was 5.2 (5.9)%. Comparing the two techniques using the method of Bland and Altman, all but one of the values were within two standard deviations of the mean difference between the methods in patients and similarly in controls.

There was a positive correlation between REE and TEE using both HR and DLW methodologies in patients and controls, the DLW data are shown in Figs 1 and 2. Using HR methodology, $TEE=0.9 REE+9$, $r=0.9$, $P=0.008$ in patients and $TEE=0.8 REE+95.7$, $r=0.7$, $P=0.006$ in controls.

There was no correlation between TEE and FEV₁ in patients ($r=0.15$, $P=0.7$) or between TEE and FFM in patients ($r=0.09$, $P=0.8$), but

Table 1 Clinical data of patients and controls

	CF subjects	Controls	<i>P</i> -value
Number	17	13	
Sex M/F	10M/7F	7M/6F	
Weight (kg)	53.0 (11.0)	63.0 (12.5)	0.09
Height (cm)	166.0 (7.9)	167.0 (8.27)	NS
BMI (kg/m ²)	19.1 (3.1)	21.8 (3.0)	0.004
FFM (kg)	31.1 (5.9)	32.6 (6.8)	NS
%FFM	62.9 (4.3) M	57.7 (7.2) M	
	54.6 (2.7) F	54.5 (4.7) F	0.04
FEV ₁ (% predicted)	52.0 (12.0)	103.0 (4.0)	<0.001

Values are means (standard deviation) BMI: body mass index; FFM: fat-free mass estimated by deuterium dilution; % FFM: per cent body weight that is fat free; NS: non-significant *P*-value.

Table 2 TEE measurements using 24-h HR and DLW in patients and controls

Subject number	TEE using 24-h HR				TEE using DLW			
	CF subjects		Controls		CF subjects		Controls	
	mean MJ/day	mean MJ/kg FFM/day	mean MJ/day	mean MJ/kg FFM/day	mean MJ/day	mean MJ/kg FFM/day	mean MJ/day	mean MJ/kg FFM/day
1	8.74	0.20	10.30	0.25	12.00	0.34	11.46	0.37
2	10.39	0.23	10.92	0.21	10.33	0.24	11.46	0.31
3	8.48	0.25	11.23	0.24	7.98	0.24	11.52	0.44
4	7.70	0.17	10.01	0.17	8.62	0.23	7.57	0.29
5	10.52	0.25	6.72	0.19	11.71	0.29	15.54	0.33
6	11.55	0.16	11.81	0.19	16.27	0.27	7.03	0.29
7	10.02	0.23	14.53	0.23	10.32	0.28	10.92	0.38
8	7.55	0.15	9.54	0.21	11.07	0.23	10.46	0.42
9	10.28	0.19	7.13	0.24	13.39	0.26	10.59	0.32
10	6.05	0.24	8.41	0.21	8.16	0.28	11.21	0.32
11	9.25	0.22	10.22	0.29	11.88	0.29		
12	9.31	0.17	8.79	0.19				
13	10.05	0.17	8.49	0.21				
14	8.35	0.20						
15	10.84	0.18						
16	14.19	0.17						
17	8.20	0.19						
mean	9.49	0.20	9.84	0.22	11.69	0.27	11.38	0.35
SD	1.85	0.03	2.07	0.03	2.79	0.04	2.71	0.05

Fig. 1 Correlation between TEE and REE in patients using doubly labelled water (DLW) data. There is a positive correlation between REE and TEE in patients using both 24-h heart rate methodology and doubly isotopically labelled water, the DLW data are shown.

Fig. 2 Correlation between TEE and REE in controls using doubly labelled water (DLW) data. There is a positive correlation between REE and TEE in controls using both 24-h heart rate methodology and doubly isotopically labelled water, the DLW data are shown.

there was a positive correlation in controls ($r=0.8$, $P=0.003$).

Resting heart rate was higher in patients, 83(7) BPM, compared to 72(10) BPM in controls ($P<0.003$). Flex heart rate also tended to be higher in patients, 100(8) BPM compared to 96(8) BPM, this was not statistically significant ($P=0.09$).

Mean physical activity levels or non-resting energy expenditure as measured by TEE/REE was higher in the control group compared to the patient group using both DLW and 24-h HR values for TEE. Using the 24-h HR values for TEE, PAL in patients was 1.2(0.1) compared to 1.3(0.1) in controls ($P=0.07$), and using the DLW

data PAL was 1.6(0.1) in patients and 1.7(0.1) in controls ($P=0.08$). There was no correlation between PAL and FFM in patients or controls ($r=0.04$ and $r=-0.05$ respectively). There was also no correlation between PAL and REE in either patients or controls ($r=0.6$ and $r=0.2$ respectively).

Discussion

This study shows that TEE was not elevated in a young adult population with CF with stable symptoms

compared to a control population and that 24-h HR underestimated TEE in both patients and controls when compared to DLW.

Employing the two commonly used field techniques there was no statistical difference between TEE in stable patients and controls. When results were expressed in MJ/day and MJ/kg body weight there was no difference in TEE between patients and controls, but when expressed in MJ/kg FFM there was a trend for TEE to be higher in controls. These findings are in agreement with the study by Spicher et al. who used 24-h HR methodology alone (10). Other conflicting studies relating to TEE in patients with CF are partly explained by whether results are expressed per kg body weight or per kg FFM. The increase in TEE noted by Shepherd et al. in pre symptomatic babies is less apparent when differences in body composition are accounted for between patients and controls (11).

Patients with CF have a lower fat mass and greater % FFM than control populations (25,26). In this study there was no correlation between FFM and TEE within the CF population, but that there was a positive correlation between FFM and TEE within the control population. It is difficult to draw clear conclusions from this in that the relationship between FFM and TEE within control populations is variable within the reported studies and the numbers in this study were relatively small (27,28). There are no data on the relationship between FFM and TEE within the CF population in the literature. A further study with larger numbers within this adolescent age group would be informative.

The other variable in the studies measuring TEE in patients with CF is age. Shepherd et al. assessed TEE in infants (11), Tomezsko et al. measured TEE in pre pubertal children (12) and the patients in the study by Spicher et al. included pre-pubertal children and young adolescents (10). Besides differences in growth rates between these different age groups, there are also differences in physical activity which may partly explain the differing results in these studies. Physical activity levels in infants are generally quite uniform, whereas even in adults without any chronic disease there is a huge variation in physical activity (29). When one takes into account the additional factor of decreasing pulmonary function in patients with CF, which has been shown to decrease physical activity then the variation of physical activity within the CF population may be even greater than in healthy adults (30).

This study supports the findings of Spicher et al. in that PAL was significantly decreased in the patients compared to healthy controls. The patients in this study had more severe lung disease than those in the study by Spicher, where the mean FEV₁ was 63(5)% predicted and in this present study mean FEV₁ was 52(12)%. The present study did not find a correlation between TEE and FEV₁, but the question remains regarding TEE in patients with severe pulmonary disease. One would

expect that in these patients physical activity is decreased even further and it is possible that there is a compensatory increase in the work of breathing in this group which counteracts this.

The REE measurements in this study were higher than predicted even in the control group. This may be due to methodological issues in that subjects came to the investigation room on the morning of the study from home, therefore the REE measurements were not true basal energy expenditure measurements. However, patients and controls were all taken directly to the investigation room so the error was minimized. This may also explain the relatively low PAL even in the control group.

DWL and 24-h HR are the most commonly used field techniques for the measurement of TEE. DLW is an isotope dilution technique based on the differing rates of disappearance of ²H and O¹⁸ from the body. ²H labels the body water pool and O¹⁸ labels both the water and bicarbonate pools, and the different elimination rates give an estimate of carbon-dioxide production (20). The technique has been shown to have an accuracy of between 2 and 4% in control populations when compared to whole body indirect calorimetry (17, 22). It is also an expensive technique and the need for mass spectrometry for analysis limits its widespread use. In addition, although extensively validated in control populations the technique has not been validated against whole body indirect calorimetry within the CF population and it is possible that the equilibration pools may differ within this population.

The twenty-four-hour HR methodology is much less expensive and is very easy to use. It is based on the principle that above a critical heart rate, the individually determined 'Flex HR', there is a linear relationship between oxygen consumption and heart rate (16, 18, 19). When compared with DLW in control populations the technique has consistently underestimated TEE (16, 19). In this present study 24-h HR also underestimated TEE compared to DLW, but the results of the present study are similar to other studies in both the patient and control group (15). Although an exercise treadmill was used as the calibration procedure in this study, because all of the subjects were familiar with the type of equipment and had frequently used it on school visits to gymnasiums, it is very unlikely that the heart rate changes in these experimental situations can duplicate exactly the cardiorespiratory changes involved in spontaneous and free-living energy expenditure patterns. This will continue to be a problem with the 24-h HR methodology, but to some extent it can be minimized by using an exercise procedure for calibration with which subjects are very familiar. In studies measuring energy expenditure in children, bicycle ergometry is sometimes used as children cycle quite a lot. In this study as in others, 24-h HR methodology may give errors in measurements in individual subjects, but gives reasonable group results within the CF

population to the extent that it could be a very useful tool in assessing activity patterns in patients with varying degrees of respiratory disease (19).

The heart-rate methodology proved to be repeatable in patients and controls. Results were in keeping with other published studies assessing the repeatability of the method in healthy volunteers (15, 20, 31). The 24-h HR method provided additional information regarding resting and flex heart rates in patients and controls. Resting heart rate levels were consistently elevated in the patient relative to the control group. This could be attributable to the catecholamine levels (32, 33), or increased work of breathing (34).

Patients and controls found both methods acceptable and non-intrusive and, although DLW has not been validated for use in this population, it does seem to be a valuable method for measuring TEE. Twenty-four-hour HR is repeatable and provides valuable additional information on physical activity levels and is more acceptable to an adolescent population despite underestimating TEE, the technique is also economically more viable for widespread use than doubly isotopically labelled water.

In conclusion this study shows that TEE is not increased in a stable population of young adult patients with CF relative to a control population despite an increase in REE. They also have reduced activity levels compared to a control population. Twenty-four-hour HR methodology has also been shown to be a repeatable and reproducible method for the measurement of TEE in patients with CF.

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