Energy balance during acute respiratory exacerbations in children with cystic fibrosis

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ABSTRACT: Acute respiratory exacerbations have been proposed to contribute to the negative energy balance which causes undernutrition in cystic fibrosis. However, no studies have measured their effect on all components of energy balance. The aim of this study was to measure the effect of an acute respiratory exacerbation on energy balance.

Fourteen children (six females, eight males, mean±SD age 9.9±2.4 yrs) were studied when well and during the course of an acute respiratory exacerbation treated with intravenous antimicrobial therapy. The total energy expenditure was measured using the doubly-labelled water method, resting energy expenditure by ventilated hood indirect calorimetry, energy intake by household measures records, and fat malabsorption from measurements of dietary fat intake and faecal fat output.

The exacerbation was associated with a significant reduction in energy intake (mean paired difference 47 kJ·kg of body weight^{-1}·day^{-1}, p<0.01). Changes in fat malabsorption and resting energy expenditure were negligible. The absence of significant changes in body weight and composition, together with the trend towards lower total energy expenditure, suggested no marked negative energy balance during the exacerbation.

In conclusion, treatment of acute respiratory exacerbation with intravenous antimicrobial therapy represents a relatively minor challenge to energy balance and nutritional status in children with cystic fibrosis.
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Undernutrition is common in children and adolescents with cystic fibrosis (CF), and it has a number of adverse clinical consequences including impairment of the lung and immune function [1, 2]. Undernutrition is the result of negative energy balance (energy intake less than the sum of the energy outputs), but the causes of negative energy balance in CF are complex and poorly understood. In particular, the relative contribution of increased energy expenditure, insufficient energy intake, and malabsorption, to undernutrition is unknown [2]. The cumulative adverse effect of acute respiratory exacerbations on energy balance has been proposed as an important element in the aetiology of undernutrition in CF [2, 3]. If confirmed, this hypothesis would require more aggressive nutritional therapy during or after acute respiratory exacerbations and/or greater emphasis on prevention of respiratory exacerbations.

A successful strategy to identify the causes of negative energy balance is to simultaneously measure all components of energy balance (energy intake, faecal losses, total and resting energy expenditure) in the same patients, and to compare these during a period of clinical stability with a period of clinical deterioration [2, 4].

In CF, acute pulmonary exacerbations are periods of clinical deterioration that are believed to have important consequences for energy balance. Energy intake might decrease, at least initially [5, 6]. Resting energy expenditure has been reported to increase temporarily in certain patients by some authors [7, 8], but not by others [9] and the effect of this on the energy requirement is unknown since total energy expenditure has not hitherto been measured during acute exacerbations. Any increase in resting energy expenditure might be offset by a decline in energy expended on physical activity, as is the case in other chronic diseases [2, 4].

The present study aimed to: 1) describe the energy balance in a group of children with CF during acute pulmonary exacerbation; and 2) measure the effect of acute exacerbation on each component of energy balance by comparing measurements made during an acute exacerbation with those made when the same child was well and clinically stable. The goal was to identify which components of the energy balance equation change during acute respiratory exacerbations.

Patients and methods

Patients and design

The aim was to study each child during a 14-day treatment of an acute respiratory exacerbation and when they were well (measurements started within 4 weeks after the end of the treatment for an exacerbation).

A respiratory exacerbation was defined as an increase in cough and sputum production, and dyspnoea, which, in the opinion of the specialist CF physicians, required *i.v.* antibiotic therapy [10]. Seven of the patients were treated with *i.v.* antibiotics only at the time of respiratory exacerbations. The others (n=7; "regular" group) had more severe disease, a history of more frequent respiratory exacerbations, and were receiving regular, usually every 2–3 month, *i.v.* therapy to prevent continuing respiratory deterioration. Children in this regular group were recruited when they presented with increased respiratory symptoms prior to regular *i.v.* antibiotic therapy.

Patients were recruited to the study on the day that antibiotic therapy began and measurements started on the following day. All patients received standard 14-day courses of *i.v.* antibiotics (usually with ceftazidime and tobramycin). Antibiotic therapy was started in hospital and completed at home in most patients, but two were hospitalized throughout the duration of the *i.v.* antibiotic therapy, because their families would not have coped with home therapy in the absence of substantial support. In addition to *i.v.* antibiotic therapy, patients received inhaled bronchodilator medication, vitamin supplements, protein-energy supplements, and pancreatic enzyme replacement therapy (PERT). One child was receiving oral corticosteroids at the time of the study. Prescribed dosages of PERT, bronchodilator therapy, nutritional supplements (except for one patient who received additional supplementary feeding during hospitalization for the exacerbation), and corticosteroids did not change during the acute exacerbation. Decisions regarding hospital admission, therapy, and discharge were made independently of the study protocol. Hospital ethics committee approval was obtained, and the research was carried out with the informed consent of patients and their families.

Clinical data

Measurements of forced expiratory volume in one second (FEV_1) were performed when each child was clinically stable and, within the first two days of the acute exacerbation. Genotypes and Shwachman scores were known for all patients. Growth and nutritional status were assessed during each period by measuring height (to 0.1 cm) on a Harpenden stadiometer (Holtain, Crosswell, UK) and weight (to 0.1 kg) on Salter digital scales (Salter, London, UK). From these measurements the body mass index (BMI; $kg \cdot m^{-2}$) and SD scores for height and BMI [11] were calculated relative to UK reference data, as currently recommended [11, 12].

Measurement of energy balance

Total energy expenditure was measured over 13–14 days in both periods, using the doubly-labelled water method [13] which is based on the differential disappearance of an oral loading dose of water enriched with deuterium (lost from the body as water) and ^{18}O (lost from the body as water plus CO_2). The difference in disappearance rates of the two stable isotopes is an accurate measure of the CO_2 production rate [13] which can be converted to total energy expenditure using a value for the energy equivalent

of CO_2 production based on a food quotient from dietary intake data [14]. Each child received a sterilized, weighed dose of 1.6 mL·kg of body weight^{-1} ^{18}O (10% enriched) mixed with 0.06 mL·kg of body weight^{-1} of 99.9% enriched deuterium oxide. Urine samples were obtained from each child before the dose was given, and on days 1, 13 and 14 after the dose. Isotopic enrichments of urine samples and diluted dose were analysed in duplicate by isotope ratio mass spectrometry (Bureau of Stable Isotope Analysis, Brentford, UK).

Resting energy expenditure was measured by ventilated hood indirect calorimetry (Datex Instrumentarium, Helsinki, Finland). In nine patients, this was carried out after an overnight (10–12 h) fast. In the other five patients, an overnight fast was not tolerated and a 4 h fast (12:00–16:00 h) prior to each measurement was agreed and used throughout. β-agonist medication was not used for the duration of the pre-test fasting period. Once a "steady state" had been reached, each child was measured for 12–20 min. The coefficient of variation for these measurements was <3% in the authors' laboratory [15], which is similar to that reported in other laboratories. Resting energy expenditure was predicted for each child on the basis of sex and age, using standard equations [16]. Measurements of resting energy expenditure were made on 2–3 occasions when the child was well and on five occasions (alternate days after recruitment) during the exacerbation. There was no evidence of systematic changes in resting energy expenditure over time during the exacerbation (repeated measures ANOVA), so in each patient the mean resting energy expenditure for each period was calculated and used as a summary measure in the energy balance determinations.

Energy and fat intakes were measured by a trained dietitian (J.M. Ralston) using prospective household measure records [17]. When a child was well, records were obtained from one weekend and two week days. During acute exacerbations, dietary records were completed on alternate days following the start of antibiotic therapy, giving a total of 6–7 day records for each patient. There was no evidence of systematic changes in energy intake over time during either study period (repeated measures ANOVA). As a result, mean daily energy intake was calculated for each patient during each period, and was used as a summary measure for the energy balance determinations. Faecal fat output was calculated from a three day stool collection made during each period, using the method of VAN DE KAMER *et al.* [18]. Changes in faecal fat output were standardized for changes in fat intake using the coefficient of fat absorption (CFA; fat absorption/fat intake).

Body composition was estimated by bioelectrical impedance using the prediction equation of HOUTKOOPER *et al.* [19] that has been validated against hydrodensitometry in Scottish children [20].

Statistical analysis

Data were summarized using standard descriptive indices for normally distributed data. Since the study employed a paired design, mean paired differences (and 95% confidence intervals (CI)) for each variable were calculated, and Students's t-tests were used to assess the statistical significance of differences between the study periods. For

the paired comparisons of energy balance variables between the periods, certain patients were excluded. Patient 4, treated for the first episode of colonization with pseudomonas, did not show objective evidence of deterioration in symptoms during the exacerbation. Patient 2 showed an unphysiological increase in energy intake during the exacerbation which was attributed to the institution of supplementary feeding in hospital.

Results

Clinical data

Clinical characteristics of the children are shown in table 1. Despite a wide range in lung function and disease severity, the group as a whole was reasonably well nourished (mean±SD BMI score -0.22±0.78) and had reasonable linear growth (mean±SD height SD score -0.59± 1.15). They were characterized by relatively stable nutritional status: mean±SD change in BMI SD score for the year prior to recruitment was 0.04±0.51. Three patients had severe lung disease (FEV_1 <40% predicted), four had moderate lung disease (FEV_1 40–70% pred), and seven had mild lung disease (FEV_1 >80% pred). Eleven patients were prepubertal, two pubertal, and one postpubertal.

Respiratory assessments (measures of lung function data, symptoms, and chest radiography findings) during acute exacerbations are shown in table 2. The data show a deterioration in lung function (in 11 of 13 patients), chest radiography (8 of 14), and clinical condition (12 of 14) in patients during an acute exacerbation. This was true for most patients whether treated with regular *i.v.* therapy or not. The change in FEV_1 % pred during an exacerbation was statistically significant (p<0.001): mean paired difference 11 (95% CI 7–16).

For the whole group, changes in body weight over the period of the acute exacerbation were small (mean gain of +0.2 kg over 14 days) and did not reach statistical significance. Weight increased in 8 of the 14 patients and

decreased in 3 of the 14, but in almost all cases changes in body weight did not exceed 1 kg. One patient (number 7) showed a weight gain of 2.0 kg during the exacerbation. Changes in body composition were also small and not statistically significant: mean±SD change in fat free mass 0.0±0.9 kg and mean change in fat mass 0.1±0.9 kg.

Energy intake

Paired differences in energy intake within each patient are shown in table 3. Energy intake was higher when patients were well, with a mean paired difference which was statistically significant (mean±SD paired difference 47±46 kJ·kg of body weight^{-1}·day^{-1}, 95% CI 15–80 kJ·kg of body weight^{-1}·day^{-1}, p<0.01). In three children, energy intake increased during acute exacerbation. In one patient (number 2) the increase was marked and was associated with supplementary nasogastric tube feeding.

Total and resting energy expenditure

There was a trend towards higher total energy expenditure when patients were well, with a mean±SD paired difference of 22±59 kJ·kg of body weight^{-1}·day^{-1} but this trend did not reach statistical significance (table 3). Differences in resting energy expenditure between study periods were negligible (table 3): mean±SD paired difference was 0±17 kJ·kg of body weight^{-1}·day^{-1}.

Faecal fat output

The CFA changed little as a result of the acute respiratory exacerbations: mean±SD paired difference in CFA was 0.03±0.05 (95% CI -0.07–0.01). Marked improvements in CFA occurred during the acute exacerbation in two patients (numbers 2 and 7).

Table 1. – Clinical and anthropometric characteristics of the subjects

Patient No.	Age yrs	Category	Genotype*	Shwachman score[+]	BMI SD score[+]	Height SD score[+]
1	9.1	S	2	90	-0.15	-1.40
2	12.3	S	1	85	0.18	0.70
3	11.0	S	1	90	-1.32	0.76
4	5.1	S	2	90	0.79	0.85
5	9.3	S	2	80	-0.98	-0.56
6	11.4	R	3	65	0.42	0.44
7	9.3	S	1	90	0.26	-0.20
8	7.6	S	2	90	-0.54	-1.20
9	7.9	R	1	75	0.31	-1.60
10	15.0	R	1	80	0.09	0.40
11	10.8	R	1	45	-1.64	-1.20
12	8.9	R	1	85	0.66	-0.58
13	8.9	R	1	65	0.01	-2.98
14	12.5	R	2	65	-1.20	-1.75
Mean	9.9			78	-0.22	-0.59
SD	2.4			14	0.78	1.15

Patients 1–6 were female and 7–14 male. BMI: body mass index; S: standard exacerbation (patients not on regular antibiotic therapy); R: exacerbation in patients treated on regular antibiotic therapy. *: 1=homozygous for delta F508, 2=heterozygous, 3=other genotype; [+]: data for period when patients were well and clinically stable.

Table 2. – Clinical data during acute respiratory exacerbation

Patient No.	FEV$_1$ % pred		ΔFEV$_1$	Weight change kg (day 1–14)	Condition[+]	Cough frequency*	Sputum volume*	Chest radiograph
	Exacerbation	Stable						
1	80	83	3	0.2	Worse	+	+	+
2	51	67	16	0.7	Worse	+	+	+
3	73	93	20	0.2	Worse	+	+	+
4	105	105	-	0.7	Similar	-	-	+
5	67	78	11	-0.7	Worse	+	+	-
6	46	NA	-	-0.3	Worse	+	+	+
7	71	82	11	2.0	Worse	+	+	+
8	89	103	14	0.5	Worse	+	+	-
9	100	100	-	0.0	Worse	+	+	-
10	69	89	20	-0.5	Worse	+	+	+
11	33	44	11	0.0	Worse	+	+	+
12	93	98	5	0.0	Similar	+	+	-
13	38	59	21	0.1	Worse	+	+	-
14	30	31	1	0.4	Worse	+	+	-
Mean	66	77	11***	0.2				
SD	23	23	7	0.7				

Patients 1–6 were female and 7–14 male. ΔFEV$_1$: change in forced expiratory volume in one second % predicted (measurement when stable exacerbation). *: clinical assessments made at the time of antibiotic therapy, +: increase in signs; -: no change, NA: measurement not available. ***: $p < 0.001$.

Discussion

This study showed that treatment of acute respiratory exacerbations in children with a range of disease severity was associated with a modest reduction in energy intake with minimal effects on resting energy expenditure and fat malabsorption. From the energy balance data (table 3) and from the fact that weight (table 2) and body composition were maintained, it can be seen that these children maintained energy balance over the course of the acute exacerbation. This suggests that the reduction in energy intake during the exacerbation was offset by a reduction in total energy expended. In this study, total energy expenditure declined during the acute exacerbation, but this difference did not reach statistical significance. Previous studies of acute exacerbations have been carried out in hospitalized patients [5–9] but, together with the present study and some recent evidence on weight changes in children treated with *i.v.* antibiotic therapy at home [21], it seems likely that the overall effect of treated acute exacerbations on energy balance is mild whether patients are treated at home or in hospital. Some degree of negative energy balance may have occurred prior to the beginning of treatment, but the absence of marked "catch up" (mean weight gain 0.2 kg) during treatment, and the evidence of long-term stability in nutritional status, implies that the

Table 3. – Energy balance data: means and paired differences

Patient No.	Energy intake kJ·kg of body weight·day⁻¹			Total energy expenditure kJ·kg of body weight⁻¹·day⁻¹			Resting energy expenditure kJ·kg of body weight⁻¹·day⁻¹				Coefficient of fat absorption		
	Exa.	Stable	Δ[+#]	Exa.	Stable	Δ[+]	Exa.	Stable	Δ[+]	Predicted	Exa.	Stable	Δ[+]
1	226	331	105		311		194	196	2	164	0.97	0.96	-0.01
2	253	164	-89	229	275	46	135	156	21	149	0.97	0.76	-0.21
3	194	195	1	280	237	-43	170	176	6	119	0.98	0.97	-0.01
4	471	436	-35	424	364	-60	224	213	-11	181		0.98	
5	264	382	118	242	250	8	174	157	-17	166	0.98	0.96	-0.02
6	261	251	-10	285	290	5	161	165	4	124	0.98	0.98	0.00
7	264	306	42	362			201	192	-9	166	0.92	0.86	-0.06
8	245	342	97	340	386	46	197	215	18	195	0.93	-	
9	328			401			231			180		0.97	
10	253	219	-34	196	210	14	123	138	15	121	0.97	0.98	0.01
11	405	430	25	274	294	20	221	218	-3	181		0.98	
12	266	330	64	307			204	166	-38	166	0.98	0.98	0.00
13	353	409	56				218	206	-12	192	0.98	0.97	-0.01
14	402	453	51	221	371	150	207	220	13	167	0.97	0.94	-0.03
Mean	288	332	47**	290	305	22	187	184	0	162	0.96	0.94	-0.03
SD	68	85	46	72	59	59	33	27	17	25	0.02	0.05	0.05

Patients 1–6 were female and 7–14 male. Exa.: exacerbation. Δ: paired differences calculated as (stable minus exacerbation); +: patient 4 was omitted from calculation of paired differences, but not group means (see table 2 and text); #: patient 2 was omitted from calculation of paired differences in energy intake (see text); **: $p < 0.01$.

magnitude of any negative change in energy balance before the study was small and not clinically significant.

Perhaps surprisingly, this is the first study to measure all components of energy balance simultaneously in children with CF, and to test the impact of a challenge to energy balance, acute respiratory exacerbation, and on each component of the energy balance equation. This study design is necessary if the causes of negative energy balance in CF are to be fully understood [2] and is based on that used successfully in the study of causes of undernutrition in other chronic diseases such as human immunodeficiency virus (HIV) infection [4]. A paired design was adopted, with each child acting as their own control, and almost all of the suitable children were recruited from the authors' large paediatric centre. Some variables could not be measured in all children because of failure of compliance. However, the sample recruited was adequate to demonstrate a significant reduction in energy intake and that there was no effect of acute respiratory exacerbation on resting energy expenditure or CFA. The trend towards reduced total energy expenditure observed would have required a sample size of >35 paired comparisons to have reached statistical significance (standardized difference of 0.40, power 0.80, at 5% level) and would have been impractical; no other clinical study using doubly-labelled water has achieved a sample size of this magnitude. As noted above, the absence of marked changes in body composition imply that the reduced energy intake must have been offset by reduced total energy expenditure, in the absence of changes in the other energy balance variables measured. The failure to demonstrate a significant change in total energy expenditure might therefore reflect the sample size available for this comparison or the fact that the total energy expenditure measure was integrated over 14 days and this may have obscured changes within this period.

The possibility that the results and conclusions might differ between those patients treated with regular *i.v.* antibiotic therapy and the rest was considered. The small sample size for this precluded statistical analysis, but despite the fact that those receiving regular *i.v.* antibiotic therapy had more severe disease (table 1) and more frequent exacerbations, marked differences between the groups were not obvious. Acute respiratory exacerbations in CF are easier to recognize than to define [10], but the statistically significant reduction in lung function supports the view that acute respiratory exacerbation was present in all patients included in the paired analyses. It is also of note that the clinical criteria for defining exacerbation in this study are identical to the main clinical features used to diagnose exacerbations in the major treatment centres in the USA [10].

The mean energy intake observed in the children studied when well (table 3), was almost 120% of the estimated average requirement for energy [22]. This and other empirical observations [23] suggest that children with CF can meet CF specific recommendations for dietary intake [24], at least when they are well. This must have contributed to the relatively good nutritional status of the sample. In most patients (10 of 14) this level of intake was achieved without the use of nutritional support when they were well and clinically stable. In four of the 14 patients regular home enteral nutrition was used when children were well (three with sip feeds, one with overnight nasogastric tube feeding), and this provided mean±SD of 22±4%

of total energy intake when well. Average energy intake fell by ~13% during the acute respiratory exacerbations. Obvious changes were unable to be identified in the pattern of dietary intake (such as changes in meal size or frequency) which were associated with this reduction in intake during the exacerbation, and to do so would probably require a more formal study directed to addressing this particular question. There was no evidence of marked under reporting of energy intake in the present study (reported energy intake <1.3-times measured resting energy expenditure [25]), and the large amount of dietary data increased the precision of dietary intake assessments [17]. Levels of total energy expenditure observed (mean 311 kJ·kg of body weight^{-1}·day^{-1}) were higher than the UK estimated average requirements for children of the same age and sex [22], and were higher than the average requirements cited in a recent review [26].

The markedly increased energy intake during acute exacerbation in patient number 2 was unexpected. This child was known to comply poorly with treatment and the improved intake during acute exacerbation (treatment was entirely in hospital, in contrast to most other patients) was attributable to the initiation of supplementary nasogastric tube feeding. Prior to the study, poor compliance with PERT was also suspected in patient numbers 2 and 7. The improvement in CFA during hospitalization, where enzyme supplementation was supervised (both patients were hospitalized for the duration of antibiotic therapy, in contrast to the other patients), supports this. In patient number 7, the marked weight gain during an exacerbation might have resulted from improved compliance with oral corticosteroids. In these two patients, changes in energy balance during the exacerbation therefore reflect hospitalization and its effect on treatment compliance rather than effects of the acute exacerbation *per se*. These data illustrate the potential importance of treatment compliance to the maintenance of energy balance, and therefore nutritional status, in some children with CF.

In conclusion, treatment of acute pulmonary exacerbations, although associated with a degree of anorexia, are less of a challenge to energy balance for the patient with cystic fibrosis than was previously suspected. This study is consistent with other recent evidence that most children with cystic fibrosis do not experience marked negative energy balance during acute respiratory exacerbation, and that this is true whether patients are treated at home [21] or in hospital [9]. This study does not support the hypothesis that treatment of acute respiratory exacerbations causes negative energy balance in children with cystic fibrosis, and suggests that alternative explanations for the causes of negative energy balance in cystic fibrosis must be sought.

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