Impact of Intravenous Antibiotic Therapy on Total Daily Energy Expenditure and Physical Activity in Cystic Fibrosis Children with *Pseudomonas aeruginosa* Pulmonary Exacerbation

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ABSTRACT

Resting energy expenditure (REE) increases during pulmonary exacerbation by *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients, and decreases after i.v. anti-*Pseudomonas aeruginosa* antibiotic therapy (IVAT). However, the impact of IVAT on total energy expenditure (TEE) is unknown. The aim of this study was to assess the changes in TEE and its main components after IVAT administered at home. Body composition measured by skinfold thickness and bio-impedance analysis, energy intake (EI) assessed by a weekly diary, REE measured by indirect calorimetry (IC), TEE assessed by a technique using 24-h heart-rate monitoring method and physical activity (PA) monitored using an activity diary (AD) were assessed in 16 patients (9 boys and 7 girls) aged 12.1 ± 2.3 y (range, 7.1–14.6 y), before and after 28 ± 4 d including a 14-d IVAT course. After IVAT, weight increased significantly by 1.9% (32.1 ± 7.5 versus 32.7 ± 7.6 kg; $p < 0.05$), while fat mass and fat free mass increased non significantly. EI increased by 4.6% ($10,797 \pm 3,039$ versus $11,320 \pm 3,074$ kJ/d; $p < 0.05$). TEE was not affected by IVAT ($7,014 \pm 1,929$ versus $7,081 \pm 1,478$ kJ/d) whereas REE decreased by 4.1% ($5,295 \pm 909$ versus $5,093 \pm 837$ kJ/d; $p < 0.05$), resulting in 9.3% increase in PA assessed by AD converted to metabolic equivalent tasks (MET) (37.0 ± 3.1 versus $40.7 \pm$

4.5 MET; $p < 0.05$). The improvement in nutritional status after IVAT is not related to a decrease in TEE, but probably to an increase in EI and a decrease of REE after IVAT. After IVAT, the reduction in REE is probably compensated by an increase in PA in CF patients. (*Pediatr Res* 54: 756–761, 2003)

Abbreviations

AD, activity diary
CF, cystic fibrosis
EE, energy expenditure
EI, energy intake
FFM, fat free mass
FM, fat mass
HR, heart rate
HRMT, heart rate monitoring technique
IC, indirect calorimetry
IVAT, i.v. anti-*Pseudomonas aeruginosa* antibiotic therapy
PA, physical activity
REE, resting energy expenditure
TEE, total energy expenditure
EE, energy expenditure

Prognosis and pulmonary function are highly correlated with nutritional status in patients with cystic fibrosis (CF) (1). Many factors, alone or combined, contribute to malnutrition in CF: 1) reduced energy intake according to recommended dietary al-

lowances (2) increased energy loss (3) increased resting energy expenditure (REE) with or without changes in total energy expenditure (TEE) (4–8). Nutritional status correlates with the severity of the disease (9), and is one of the central considerations in CF management (3). In 50% of CF patients, chronic pulmonary infection by *Pseudomonas aeruginosa* is present and may also play a role in malnutrition (10–12). Previous studies have shown that i.v. anti-*Pseudomonas aeruginosa* therapy (IVAT) can improve nutritional status, but the mechanisms underlying this phenomenon are not well understood (13–16). Any increase in REE and/or TEE in CF patients, at

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baseline and/or during pulmonary exacerbation, is important because it may contribute to a negative energy balance and malnutrition.

Total energy needs comprise the summation of energy required at rest (50% to 60%), for exercise (30% to 40%), for food metabolism, and for growth in children (17). Several authors have reported REE in CF patients to be 10% to 30% higher than predicted (15, 18–22) or than in controls matched for age, sex, and weight (23, 24). Mechanisms leading to increased REE may include the genetic defect underlying CF, the energy cost of breathing, and the systemic effects of excessive chronic pulmonary inflammation (24, 25) and it has been shown that REE decreases after IVAT (15, 26–28). The impact on TEE of IVAT used to treat *Pseudomonas aeruginosa* pulmonary exacerbation is unknown. The aim of the present study was to assess the changes in TEE, REE, and physical activity after home-administered IVAT.

PATIENTS AND METHODS

Patients. The study was carried out during years 1999 to 2001. During this period, the Cystic Fibrosis Center of Lille followed 122 CF patients. CF patients were selected for the present study if they were aged between 5 and 18 y, were chronically colonized with *Pseudomonas aeruginosa* (the presence of *Pseudomonas aeruginosa* in three consecutive sputum analyses over a 6-mo period). Noninclusion criteria were cardiac insufficiency, cardiac rhythm abnormalities, treatment with beta-blockers, oxygen therapy, and lung transplantation. Patients were excluded from the study if they required hospitalization, treatment with corticosteroids, or presented with any acute condition (such as extra-pulmonary infection) known to interfere with energy expenditure (EE), during the study period. From this population, 34 patients met the selection criteria. All 34 were contacted to participate at the study and finally 16 were included when they required home IVAT for pulmonary exacerbation (presence of *Pseudomonas aeruginosa* in sputum analyze) and a Smith score higher than 5/10 (29). Six children refused to participate, 8 were not included because they received antibiotics course during school summer holidays (and could not be studied during a school day), and 4 could not be included for technical reason (equipment for the study not available at the time of their antibiotic courses). The sixteen children and adolescents with CF included were 9 boys and 7 girls aged 12.1 ± 2.3 (mean $\pm$ SD) years (range, 7.1–14.6 y) with a mean Shwachman score of 75 ± 10 (median: 80 range: 65–90) and a forced expiration volume in 1 s of $67 \pm 25\%$ of theoretical values. At inclusion in the study, Z-score for weight/height was above -2 SD (mean: -0.3 ± 1) according to French population (30) for all patients, but only one who was slightly malnourished (Z-score: -2.3).

All procedures were performed in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. Before the study began, the purpose and the objectives were carefully explained to participants. Written informed consent was obtained from both children and parents, and the study was approved by the Lille University Ethics Committee

(Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lille).

Study protocol. Each subject was studied twice 3–7 d before the administration of IVAT, and 5–10 d after the completion of the 14-d IVAT. During the first visit to the hospital, the child underwent body composition assessment, REE measurement, and calibration of energy expenditure with heart rate. At that time, the 7-d food record was reviewed by the same dietitian. The following day, heart rate and physical activity recorded by activity diary were monitored for 24 h under normal lifestyle conditions during a school day without sporting activity. During a second hospital visit one week after the completion of the 14-d home IVAT (so, 28 ± 4 d after the first visit), the food record, body composition, REE, and the calibration equation for heart rate and energy expenditure were again assessed, 28 ± 4 d after the first evaluation. The following day, HR and PA were simultaneously recorded for 24 h on the same school day of the week as the first evaluation.

Analysis of energy expenditure. The two visits were as followed: on the day of the test, the child arrived by car at the Clinical Research Center of the Lille University Heart Hospital (CIC-9301-INSERM-CHU) at 08:00 h, having fasted from 20:00 h on the previous day. The child then rested recumbent on a hospital bed watching a videotape. The same quiet cartoon of 1h 30 min duration was used for all the children. As the adaptation period was 15 min under the ventilated canopy system and REE was measured for 30 min, children watched the same cartoon during the two sessions: the first 45 min were seen during the first session before IVAT and the last 45 min during the second session after IVAT.

Oxygen consumption ($\dot{V}O_2$ in mL/min) and carbon dioxide production ($\dot{V}CO_2$ in mL/min) using the validated instrument Deltatrac II (Datex Instrumentation Corporation, Helsinki, Finland) were measured every minute. The validity and accuracy of expired carbon dioxide ($\dot{V}CO_2$) and inspired oxygen ($\dot{V}O_2$) flows, the respiration quotient (RQ), and flow settings were calibrated every 6 mo with reference to alcohol combustion by the manufacturer of the calorimeter. The manufacturer certified a coefficient of variation (CV) of $<2\%$ for each measurement of $\dot{V}CO_2$ and $\dot{V}O_2$ flows and the RQ. Values automatically selected to compute individual REE using the Weir formula were those for which the CV was less than 10% for both $\dot{V}O_2$ and $\dot{V}CO_2$, and was less than 5% for RQ (31–33). Values with a higher variation were automatically excluded from REE computing by the “built in sensitive artifact algorithm” of the Deltatrac II. This procedure gave a CV less than 6% for REE measurement. In our study, the CV of REE measurement in the same set for one subject using Deltatrac II was indeed less than 5% (4.92 ± 1.33 before versus 4.86 ± 1.24 after IVAT; $n = 16$; during 30 min of measurement). The intra-subject CV of REE measurement by Deltatrac II has already been evaluated in control by Molnar and Schulze and was less than 3% (34). Inter-subject CV of repeated REE measurement has also been evaluated in 8 consecutive sets of measurements in 12 infants by Schulze *et al.* and was 5.6% (35).

TEE was assessed using the heart-rate monitoring technique (HRMT) calibrated against indirect calorimetry, according to a recently published procedure (36, 37). Briefly, the child was

fitted with probes for the continuous recording of heart rate (HR) using a silver/silver chloride electrode, with a Holter 24/48-h recorder with two channels for electrocardiographic data (Synesis, ELA Medical, Montrouge, France). The calibration period included different activities such as resting; the postprandial period 1 h after a nonstandardized breakfast of 1500 ± 400 kJ, corresponding to 20% of daily energy requirements for each child (38); and at different levels of physical activity on a cycle ergometer (Philips, Paris, France), beginning at 0 W and increasing the braking force (by 2.5 W every 30 s for children <12 y, and by 2.5 W every 30 s for children >12 y) to achieve a maximal HR close to the theoretical maximal heart frequency ($220 - \text{age in years}$). This calibration period was used to define an individual regression equation between the HR and EE data. The HR values, defined as the mean of the HRs recorded every minute over the specified periods, were calculated with Synetec software (version 1.1; ELA Medical, Montrouge, France). Several equations using the relationships between HR and EE have already been tested in the literature as in our laboratory (36, 37, 39). Equations tested were linear or polynomial. The best fit describing the relationship of HR to EE was obtained by a polynomial third equation curve (P3): $EE = a \times HR^3 + b \times HR^2 + c \times HR + d$, (where a, b, c, and d are numeric factors) determined for each subject on the basis of the measurements made at rest, during the postprandial period, and at different levels of physical activity. Mean coefficient of regression "r" of each individual P3 equation before and after IVAT were very close to 1 indicating a good fit (0.98 ± 0.02 versus 0.98 ± 0.02). Secondly, the smaller mean standard residuals between HR and EE were obtained with the P3 equation (0.02 ± 0.01) indicating the best fit of this mode of calculation. HMRT method provides a close estimation of TEE with an accuracy of about 2.5% compared with whole-body calorimetry (40). Previous studies have shown that the precision of calculated TEE using the HRMT is good with a CV less than 5% as 4.0% by Livingstone *et al.* (41) and 4.7% by Bitar *et al.* (42). This precision under 5% is acceptable for determining TEE for individuals. This method has also been validated against the doubly labeled water method and was found suitable for CF patients (7).

Body composition analysis. Weight and height were first measured, then body composition was assessed by both impedanceometry and skinfold thicknesses. The child then rested recumbent on a hospital bed for 15 min. Body resistance was measured using a body impedance 50 Hz meter (BIA 101/S, RJL Systems, Detroit, MI, U.S.A.), and fat free mass (FFM) was calculated with the Schaefer formula using left skinfold thicknesses (43). Triceps, biceps, subscapular, and suprailiac skinfold thicknesses were measured to the nearest 0.1 mm using a Harpenden caliper (Holtain, Crymlich, UK) according to standard anthropometric measurement previously described (44). Fat mass (FM) was calculated using the Brook formula for children under 12 y and the Durnin and Rahaman formula for children over 12 y (45, 46). These two techniques have previously been validated against dual x-ray absorptiometry in children (47).

The precision of body fat measurement using skinfold thicknesses is dependent upon the skill of the anthropometrist and the site measured. In general, an intraindividual CV within 5% can be attained easily by a properly trained and experienced individual (48). All measurements of skinfold thickness in the present study was made by the same operator (LB) who is well experimented with this technique and has a CV under 5% in this technique. The precision of fat free mass measurement using bio-impedance analysis 2% (49). As any estimate of body composition is limited by technical reasons and/or equation used, we decided to calculate FM and FFM as the mean of values obtained by both methods.

Analysis of physical activity. Physical activity was measured by an activity diary. This method has been validated against DLW as a reference method (50) and gives similar data than HMRT for the assessment of 24-h TEE (51). Children and/or participating parents filled a specific chart report form. This chart was separated in 3 portions of the day: morning, afternoon and evening. All children and/or participating parents were instructed to keep detailed self-reports on the types of behaviors and the times at which these active behaviors began and ended during the 24-h period when an accelerometer and HR monitor were worn simultaneously. A trained staff member (LB) reviewed the self-report sheets and discrepancies were resolved with the parent and child. Activity was converted to multiples of resting metabolic rate using metabolic equivalent tasks (MET) from the compendium of physical activities (52).

Analysis of energy intake. The assessment of energy intake was performed using an estimated dietary record technique as previously described (53). The technique used a specific chart report form on paper. The chart included the date, patient identity, and how to record the foods consumed: the explanations were a size instrument such as graduated bowls, cups, dishes, number of spoons. Then, each page corresponding to one day was separated in four parts: breakfast, lunch, dinner, and the nibbling. Lunch and dinner detailed in starter, main course, and desert. Both oral and written instructions were given to each patient and/or parents on how to keep accurate records using the size instrument, and the parents assisted the children in recording, identifying, and quantifying the foods consumed. Subjects recorded detailed daily food intake on the specific chart report form during 7 d.

The same dietitian reviewed each specific chart report. Quantity of all meals and drinks were checked with the same dietitian, the parents and the child together. The dietitian was well trained to identify both miss- and over-reporting and plausibility of food recording. The portion sizes were estimated using a three-dimensional portion size instrument with French current meal food photographs corresponding to an exact quantity of foods (54). All quantity was then calculated using BILNUT software (version 6; Paris, France), which computes energy intake using French foods composition tables (55). This method has been shown to provide unbiased records of energy intake in lean subjects up to 9 y old (56, 57) and showed that children aged 8–15 y were able to estimate food quantity to within $\pm 10\%$ of the amount really eaten, suggesting that

Table 1. Evolution of weight, fat free mass, fat mass and energy intake in 16 CF patients (mean $\pm$ SD)

Mean $\pm$ SD	Before	After
Weight (kg)	32.1 $\pm$ 7.5	32.7 $\pm$ 7.6*
Fat free mass (kg)	26.7 $\pm$ 6.5	27.1 $\pm$ 6.5
Fat mass (kg)	5.7 $\pm$ 2.3	6.3 $\pm$ 2.7
Energy intake (kJ/d)	10,797 $\pm$ 3,039	11,320 $\pm$ 3,074*

* $p < 0.05$ (Wilcoxon rank test).

children could quantify their food intake with reasonable accuracy (57).

Statistical analysis. Variables were compared using the paired nonparametric Wilcoxon rank test (where differences were defined as significant at $p < 0.05$) using SPSS software (SPSS 7.0 for Windows; Chicago, IL, U.S.A.).

RESULTS

All 16 patients completed the study. The evolution of their physical characteristics (weight, FFM, FM) and energy intake before and after IVAT are shown in Table 1. After IVAT, weight increased significantly by 1.9% (32.1 $\pm$ 7.5 versus 32.7 $\pm$ 7.6 kg; $p < 0.05$) while fat mass and fat free mass increased non-significantly by 6% and by 1.5% respectively. Energy intake expressed as the daily mean calculated from data collected over 7 d increased significantly by 1.9% (10,797 $\pm$ 3,040 versus 11,320 $\pm$ 3,074 kJ/d; $p < 0.05$) after IVAT. No correlation was found between evolution of weight and energy intake.

Table 2 shows the evolution of $\dot{V}O_2$, $\dot{V}CO_2$, RQ, TEE, REE, TEE/REE, and physical activity before and after IVAT. One subject was omitted from the analysis of TEE because of technical problems with the Holter record. One subject was excluded from the analysis of AD because it was not sufficiently detailed. $\dot{V}O_2$, $\dot{V}CO_2$, and RQ were stable after IVAT. REE decreased by 4.1% (5,295 $\pm$ 910 versus 5,093 $\pm$ 837 kJ/d; $p < 0.05$), whereas TEE remained stable as well as the ratio TEE/REE.

Physical activity assessed by activity diary significantly increase by 9.3% (37.0 $\pm$ 3.1 versus 40.7 $\pm$ 4.5 MET; $p < 0.05$). Figure 1 summarizes the changes in energy expenditure and physical activity.

DISCUSSION

The present study confirms previous data that showed a significant weight gain after IVAT (13, 14, 16). However we did not observed any significant change in body composition. Bio-impedance analysis and skinfold thicknesses are probably too rough method to see small differences in body compartment. That is the reason why we did not see any difference in FM and FFM between before and after IVAT. In our study, energy intake increased after IVAT and remained higher than TEE before and after IVAT (36.8 $\pm$ 24.3 versus 37.5 $\pm$ 26.5%) to compensate energy losses and fat malabsorption as recommended by Turck and Michaud (1).

The nature of the study design could not allow to allocate full causality to antibiotic treatment. Indeed, for ethical evident reasons it was impossible to perform this study on a double

Table 2. Evolution of metabolic parameters and physical activity in 16 CF patients (mean $\pm$ SD)

Mean $\pm$ SD	Before	After
$\dot{V}O_2$ at rest (L/min)	186.6 $\pm$ 30.9	184.0 $\pm$ 31.3
$\dot{V}CO_2$ at rest (L/min)	155.1 $\pm$ 27.4	152.7 $\pm$ 24.7
RQ at rest	0.83 $\pm$ 0.06	0.83 $\pm$ 0.04
REE (kJ/d)	5,295 $\pm$ 909	5,093 $\pm$ 837*
TEE (kJ/d)	7,014 $\pm$ 1,929	7,081 $\pm$ 1,478
TEE/REE	1.34 $\pm$ 0.21	1.39 $\pm$ 0.23
Physical activity (MET/d)	37.0 $\pm$ 3.1	40.7 $\pm$ 4.5*

* $p < 0.05$ (Wilcoxon rank test).

blind randomized study: patients were infected and required antibiotics for standard care, and in this case the use of i.v. placebo at home on central line seems no ethical, particularly in children. However, the improvement of the patients' course, particularly the observed increased in food intake, could not be explained just by study participation or by the fact that CF patients felt better after IVAT and recorded food more completely than before IVAT. The dietitian was indeed well trained to identify both miss- and over-reporting and plausibility of food recording. Energy intake of CF patients is currently assessed in the Cystic Fibrosis Center of Lille as in other CF centers during their usual medical follow-up and patients are used to fill such food questionnaire so that risks of methodological bias were very limited. Moreover, 2 of these subjects showed a 1.6% and a 27.4% reduction of energy intake compared with the first food questionnaire at the beginning of the study.

Since TEE did not change significantly after IVAT, the improvement in the nutritional status (weight gain) could be due both to a spontaneous increase in energy intake and a decrease in REE. The mean increase in EI was 523 kJ/d after IVAT, corresponding to 14644 kJ for the entire study period (28 $\pm$ 4 d) that could partially explain weight gain. Indeed, the increase of 0.6 kg of fat mass requires 20900 kJ.

Our study shown a significant decrease of REE after IVAT. The beneficial role of IVAT on REE has already been widely documented in CF patients (27, 58). The accuracy of our REE measurement could be checked by the RQ measurement (RQ). Mean RQ measured by indirect calorimetry at rest was similar

Figure 1. Changes in total energy expenditure, resting energy expenditure, and physical activity before and after IVAT in 16 CF patients. * $p < 0.05$ (Wilcoxon rank test).

in the two sessions (Table 2). RQ at rest of 0.83 and 0.83 (before and after IVAT, respectively) were in agreement with previous data published for cystic fibrosis patients (59). This finding suggested that CF patients have a normal fasting metabolism and are able to mobilize fat store and oxidized fatty acids after a overnight fast, as controls (60–62). It has been suggested that increased REE in CF patients could be partly due to the genetic defect underlying CF, and secondarily to the energy cost of breathing and the systemic effects of chronic pulmonary inflammation (24). Cystic fibrosis patients has high level circulating inflammation markers at basal state (63) and the significant decrease of REE observed before IVAT could be attributed to a decrease of inflammation as already shown by Burdet *et al.* (58)

Studies of TEE in clinically well CF patients gave conflicting results. Using the doubly-labeled water method, one study showed an increase of 25% in TEE, although previous work using the HMRT method showed that free-living 24-h TEE values were similar in stable CF patients to those of control subjects matched for gender, age, height, and nutritional status (7, 21). To the best of our knowledge, there are no published data on the effects of IVAT on TEE. Previous studies showed a mean TEE/REE ratio of 1.55 in 13 CF patients in free-living conditions (7, 21). Our study shows a comparable but slightly lower ratio TEE/REE of 1.34 before and 1.39 after IVAT (Table 2). This can be explained by the experimental design of our study: the 16 CF patients we studied were evaluated during a school day without sportive activities, so that physical activity level of our patients could be slightly lower than those of Spicher *et al.* (21). Our results show that TEE remains stable before and after IVAT although an increase in physical activity was demonstrated by using an activity diary. Analysis of the type of PA in the AD showed that patients are more willing to participate in PA after than before IVAT, probably as a result of their improved aerobic fitness. When patients are studied after IVAT, there was no evidence of the alteration in physical activity levels that is often attributed to CF (6, 8). This spontaneous increase in physical activity is probably beneficial, and may contribute to good nutritional status, an improvement of the quality of life, cardiopulmonary fitness, and bone mineral density.

CONCLUSION

In conclusion, both the decrease in REE and the improvement in lung function after IVAT promote physical activity in CF patients, and are therefore helpful in reducing the effects of an inactive lifestyle, as is recommended by most CF referral centers (64). The quality of life of CF patients usually improves after IVAT, which contributes to an improvement in their survival and well-being. The impact of IVAT on the energetic cost of physical activity and the quality of life remains to be determined.

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