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Resting energy expenditure and lung disease in cystic fibrosis

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Abstract

Optimal nutritional support is considered to be an integral part in the management of cystic fibrosis (CF). Several factors contribute to increased resting energy expenditure (REE), which itself can lead to energy imbalance and thus contribute to deterioration of the nutritional status. We aimed to assess the impact of lung parenchyma damage on REE and correlated these findings with forced expiratory volume in 1 s (FEV_1). Twenty patients performed respiratory function testing (FEV_1), pulmonary high-resolution computed tomography (HRCT) and assessment of REE with open circuit indirect calorimetry. HRCT was scored by using a modified Bhalla method. Mean HRCT score was 8.4 and mean REE value was 108.4% predicted vs. 96.5% predicted of 16 healthy subjects ($P<0.01$). There was a significant correlation between HRCT score and REE ($P<0.01$), HRCT score and FEV_1 ($P<0.001$) and REE and FEV_1 ($P<0.05$). The correlations demonstrate a close correlation between lung damage and elevated REE in people with CF. Prevention of negative energy balance is an important part in follow-up of patients with CF. Any increase in REE should raise suspicion of progress in lung impairment.

Keywords: X-Ray tomography; Calorimetry; Lung disease; Spirometry; Disease progression; Cystic fibrosis

1. Introduction

Optimal nutrition is a major cornerstone in the management of cystic fibrosis (CF). Long term follow-up of CF patients has shown significantly better survival in patients who achieved normal nutritional status [1]. The gold standard for determining individual energy needs in patients with CF is resting energy expenditure (REE) measured by indirect calorimetry. REE in CF patients is increased due to repetitive lung infections and lung inflammation [1], increased respiratory effort and possibly as a direct result of the underlying genetic abnormality [2]. Total energy expenditure though can remain normal due to reduced physical activity [1].

Pulmonary high-resolution computed tomography (HRCT) has been considered as the most promising imaging technique to assess pulmonary architectural abnormalities in patients with CF [3–5].

To answer the question whether there is a correlation between lung disease and resting energy expenditure, we examined our patients with indirect calorimetry, and correlated these findings with HRCT score and forced expiratory volume in 1 s (FEV_1, % predicted).

2. Materials and methods

Haukeland University Hospital serves as a regional centre for CF patients in Western Norway. The study included 20 patients (10 females) from our cohort of patients with CF with a mean age of 14 years, S.D. 7 years, range 6–34 years and a median of 12.5 years. The CF diagnosis was made by demonstration of repeated elevated sweat chloride concentrations and typical clinical manifestations in all patients. Eight patients were found to be homozygous for the dF508 mutation (40%); the remaining 12 patients did either have two other mutations (3 patients), one detectable mutation (4 patients) or no mutation has been found so far (5 patients). All patients had received conventional therapy for CF for at least 6 months and they were in clinically stable condition.

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Table 1
General patient data, mean values ± S.D. Ranges in parentheses

	$N=20$
Chloride sweat in mmol/l	101 ± 22 (62–138)
Body mass index, kg/m^2	17.3 ± 3 (12.6–25.8)
Shwachman–Kulczycki score Range 4–100	73.8 ± 17.3 (28–93)
FVC—forced vital capacity in percent of predicted	92.3 ± 20.9 (47–126)
FEV_1—forced expiratory volume in 1 s in percent of predicted	78.2 ± 22.6 (25–112)

Data were collected between February 1999 and August 2000. Informed consent was obtained from patients and/or their families. The regional ethics committee approved our study protocol.

General patient data, characterizing our study population, are shown in Table 1.

Our patients attend the outpatient department every 2nd–3rd month, or more often when needed. Seven patients (35%) have chronic lung infection with *Pseudomonas aeruginosa* and they have been given 12-day courses of intravenous antibiotic treatment every 3rd month.

We performed standard computerised open-circuit indirect calorimetry (Sensor Medics Vmax, USA) after 12 h fasting, with at least 4 h restriction of using β-2 inhalative agents. The patients were placed under the canopy hood in a relaxed, supine position. Respiratory gas exchange was monitored for 10 min to allow acclimatisation, a subsequent 20-min measurement period was used to calculate REE based on the abbreviated Weir formula [6].

Pulmonary HRCT was performed the same day (General Electrics, HiSpeed CT) using 1-mm-thin sections and 10-mm intervals during inspiration, followed by 1-mm-thin sections with 20-mm intervals during expiration. A paediatric radiologist evaluated the HRCT images, and classified the findings according to a modified scoring system based on Bhallas and colleagues [7]. The morphological criteria were based on description of localisation and degree of pathological changes. According to Bhalla we evaluated bronchiectasis, peribronchial thickening, mucus plugging, sacculations, bullae, emphysema and collapse or consolidation. The scoring system was extended in terms of mosaic perfusion according to Helbich and colleagues [4]. The maximal obtainable score was 27.

Clinical status was evaluated by using a Shwachman–Kulczycki score [8]. Standard spirometry was assessed by Sensor Medics Vmax (USA) equipment.

We also examined 16 healthy subjects (7 female, median age 12 years, range 8–33 years) with indirect calorimetry in order to verify our predicted values of REE.

Data analysis was performed using a commercially available software package (SPSS). Descriptive statistics included mean, minimum and maximum values, S.D. and median. Differences in REE (% predicted) between healthy subjects and CF patients were tested using a Student's *t*-test and a Wilcoxon–Mann–Whitney test. The relation between HRCT score and REE (% predicted), HRCT score and FEV_1 (% predicted) and REE (% predicted) and FEV_1 (% predicted) were assessed by the Pearson correlation coefficient. All reported *P* values are two-tailed and $P<0.05$ was considered significant.

3. Results

The mean HRCT score in our CF group was 8.4 ± 6.1 (S.D.) ranging from 1 to 22 (median 7.5). Bronchiectasis was the most frequent finding (17 of 20 patients, 85%). Bronchiectasis were graded as mild in ten, moderate in five and serious in two of these 17 patients. Peribronchial thickening was the second most common finding and was found in 15 patients (75%); all of them were graded as mild. Mucus plugging was present in 14 patients (70%), eight patients had mucus plugging in 1–5 bronchopulmonary segments, one patient had mucus plugging in 6–9 segments and five patients in more than nine segments. Moreover, we detected consolidations in 12 patients, sacculations in 6 patients, mosaic perfusion in 6 patients and bullae in 2 patients. No patient had abscesses or emphysema. None scored zero.

The mean value of resting energy expenditure was 108.4 ± 15.4% predicted in our CF population. In healthy subjects a mean value of 96.5 ± 8.7% predicted was found, which was significantly lower ($P<0.01$). CF patients, homozygous for the dF508 mutation had a mean REE of 112.3% predicted (S.D. 10.8), the remaining patients had a mean REE of 105.8 (S.D. 17.9). This difference, however, was not statistically significant. Individual results of HRCT score, REE (% predicted), FEV_1 (% predicted) and chronic *Pseudomonas aeruginosa* infection are presented in Table 2.

There was a significant correlation between HRCT score and REE (% predicted, $r=0.661$, $P<0.01$). Fig. 1 shows the correlation between REE (% predicted) and HRCT score. High resting energy expenditure was correlated with high HRCT score.

Furthermore, there was a significant negative correlation between HRCT score and FEV_1 (% predicted, $r=-0.851$, $P<0.001$; Fig. 2).

There was as well a weak, yet significant correlation between REE (% predicted) and FEV_1 (% predicted) with $P<0.05$ ($r=-0.454$) (Fig. 3).

4. Discussion

We have found significant correlation between pulmonary HRCT findings, scored with a modified Bhalla

Table 2
Individual results in 20 patients with cystic fibrosis and mean (S.D.) values

Patient	Age (years)	HRCT Score	REE (% pred.)	FEV_1 (% pred.)	PSA[a]
1	6	5	109	99	−
2	8	10	103	73	+
3	8	1	81	85	−
4	8	7	119	78	−
5	9	8	110	82	−
6	10	3	117	95	−
7	12	9	99	74	−
8	12	15	103	65	+
9	12	7	121	71	−
10	12	15	120	55	+
11	13	1	89	98	−
12	13	5	87	101	−
13	13	1	100	112	−
14	17	8	120	109	−
15	17	9	119	69	+
16	17	22	132	25	+
17	21	3	105	91	−
18	22	4	88	84	−
19	23	15	106	37	+
20	34	19	140	61	+
Mean (S.D.)	14±7	8.4±6.1	108.4±15.4	78.2±22.6	7 (35%)

[a] PSA = chronic *Pseudomonas aeruginosa* lung infection.

score, REE and lung function as measured by FEV_1 in CF patients. Moreover, REE correlated significantly with FEV_1. Thus there seems to be an impact of lung pathology on resting energy expenditure.

Pulmonary HRCT permits evaluation of the lung parenchyma abnormalities in detail [4,9]. Even minor morphologic changes in serial CT scans before and after treatment of acute pulmonary exacerbation can be evaluated [10]. HRCT scans confer complete information of the distribution and severity of lung damage [11] and scoring of the pathological findings carry the opportunity to quantify structural lung damage.

According to previous investigations, chronic pulmonary inflammation, which leads to deterioration of the lung function, is the major factor associated with increased REE in patients with CF [1,12]. Once FEV_1 falls below 75% of predicted values, the REE raises in a curvilinear (quadratic) fashion [13]. Little, if any increase in REE is seen in well-nourished CF males with well-preserved lung function [13], although Bowler and colleagues showed increased REE in CF patients with mild lung involvement [14]. The degree of parenchymal lung damage seems to play a major role in the interaction between increased REE and lung function as measured as FEV_1.

REE decreases significantly during intravenous antibiotic treatment in patients chronically infected with *Pseudomonas aeruginosa* [15,16]. This may indicate that lung infection is the denominator in the interrelationship between lung damage and REE. The increased energy expenditure returns to pre-treatment levels some weeks after the infection has been treated [1]. We have observed similar trends (unpublished data). According to Stallings [17], treatment of acute pulmonary exacer-

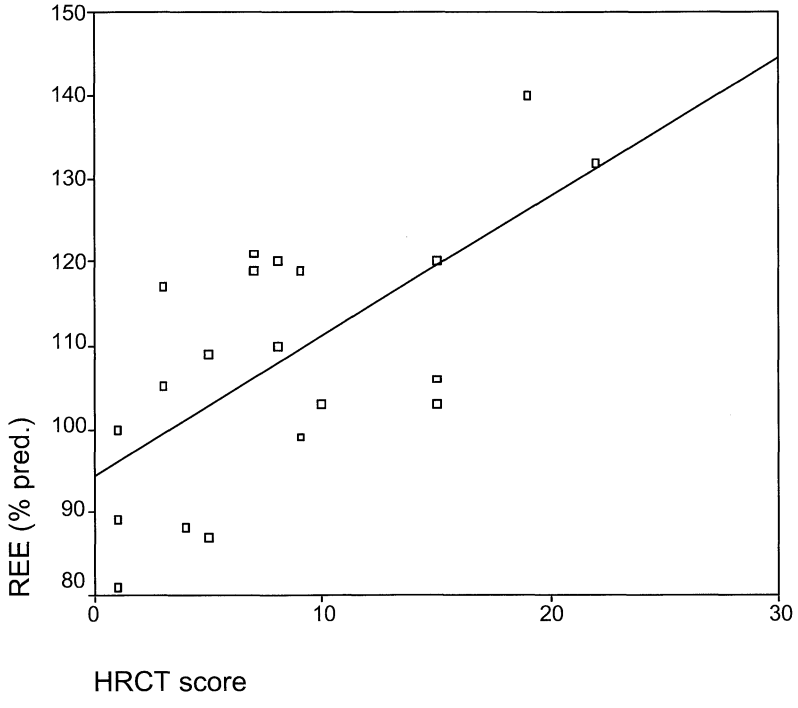

Fig. 1. Correlation between resting energy expenditure percentage predicted (REE, %predicted) and HRCT score ($r=0.661$, $P<0.01$); the graph reflects a regression line.

bation in children with mild to moderate lung disease is not associated with increase above baseline REE. However, lung function as measured by FEV_1 is improving significantly after treatment [17].

Increased REE has been reported in CF patients, homozygous for the dF508 mutation [8,18], and in patients who are colonised with *Pseudomonas* species. [19]. We found a higher mean REE in our homozygous dF508 patients though not statistically significant. This may be due to limited number of patients. Pencharz [1] and Wilson [20] have concluded from their investigations that the genetic defect itself appears to have a minor, if any effect on REE.

We found a significant negative correlation between HRCT score and FEV_1 (% predicted) in our patients. This is in accordance with previously reported findings [3,21].

To our knowledge, the correlation between resting energy expenditure and HRCT scan findings in patients with CF has not been reported before. It indicates a close relation between lung damage and caloric requirement reflecting the complex interaction between lung inflammation, bacterial infection, malnutrition and possibly the nature of the mutation in a vicious circle in CF patients. During the last 15 years, it has become increasingly clear that nutritional status has an impact on lung disease and lung function in CF patients [22]. This connection is demonstrated also in our study. We have shown a significant correlation between lung function as measured by FEV_1, and both HRCT score and REE. Several factors play their part in these complicated interactions, and we think that the inflammatory processes in the lungs are important. Investigating markers of inflammation and correlating them with REE would be of particular interest, and we intend to look at these aspects in the near future.

In addition to increased energy losses due to the exocrine pancreatic insufficiency, higher energy consumption could be explained by the interactions described in this paper, and these factors altogether make a basis for the concept that patients with CF need to have a high-energy intake.

Our findings may contribute to additional information regarding the destructive process in the CF lung, which was excellently demonstrated by Schöni and colleagues [23]. They defined lung damage from underlying disease and weight loss as crucial components in the pathogenesis of lung destruction. Focus of intervention should therefore concentrate on both components as early as possible.

Prevention of a negative energy balance is an important part of the surveillance of the patients with CF. One should therefore be aware of progress in lung impairment when increased REE is found.

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References

[1] Pencharz PB, Durie PR. Pathogenesis of malnutrition in cystic fibrosis, and its treatment. Clin Nutr 2000;19:387–94.
[2] Buchdahl RM, Cox M, Fulleylove C, Marchant JL, Tomkins AM, Brueton MJ, et al. Increased energy expenditure in cystic fibrosis. J Appl Physiol 1988;64:1810–6.
[3] Demirkazik FB, Ariyürek OM, Öycelik U, Göcmen A, Hassanabad HK, Kiper N. High resolution CT in children with cystic fibrosis: correlation with pulmonary functions and radiographic scores. Eur J Radiol 2001;37:54–9.
[4] Helbich TH, Heinz-Peer G, Eichler I, Wunderbaldinger P, Gotz M, Wojnarowski C, et al. Cystic fibrosis: CT assessment of lung involvement in children and adults. Radiology 1999;213:537–44.
[5] Mason AC, Nakielna BEM. Newly diagnosed cystic fibrosis in adults: pattern and distribution of brochiectasis in 12 cases. Clin Radiol 1999;54:507–12.
[6] Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109:1–9.
[7] Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, et al. Cystic fibrosis: scoring system with a thin-section CT. Radiology 1991;179:783–8.
[8] Shwachman H, Kulczycki LL. Long term study of 105 patients with cystic fibrosis. Am J Dis Child 1958;96:6–10.
[9] Santamaria F, Grillo G, Guidi G, Rotondo A, Raia V, de Ritis G, et al. Cystic fibrosis: when should high-resolution computed tomography of the chest be obtained? Pediatrics 1998;101:908–13.
[10] Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. High resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. Pediatr Radiol 1999;29:731–5.
[11] Tiddens HAWM. High resolution CT: how does it affect clinical management. European CF congress Vienna 2001;S9.2
[12] O'Rawe A, McIntosh I, Dodge JA, Brock DJ, Redmond OA, Ward R, et al. Increased energy expenditure in cystic fibrosis is associated with specific mutations. Clin Sci 1992;82:71–6.
[13] Fried MD, Durie PR, Tsui LC, Corey M, Levison H, Pencharz PB. The cystic fibrosis gene and resting energy expenditure. J Pediatr 1991;119:913–6.
[14] Bowler IM, Green JH, Wolfe SP, Littlewood JM. Resting energy expenditure and substrate oxidation rates in cystic fibrosis. Arch Dis Child 1993;68:754–9.
[15] Steinkamp G, Drommer A, von der Hardt H. Resting energy expenditure before and after treatment for *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Am J Clin Nutr 1993;57:685–9.
[16] Peckham D, Leonard C, Range S, Knox A. Nutritional status and pulmonary function in patients with cystic fibrosis with and without *Burkholderia cepacia* colonisation: role of specialist dietetic support. J Hum Nutr Diet 1996;9:173–9.
[17] Stallings VA, Fung EB, Hofley PM, Scanlin TF. Acute pulmonary exacerbation is not associated with increased energy

expenditure in children with cystic fibrosis. J Pediatr 1998;132:493–9.
[18] Thomson MA, Wilmott RW, Wainwright C, Masters B, Francis PJ, Shepherd RW. Resting energy expenditure, pulmonary inflammation, and genotype in the early course of cystic fibrosis. J Pediatr 1996;129:367–73.
[19] Vinton NE, Padman R, Davis M, Harcke HT. Effects of *Pseudomonas* colonisation on body composition and resting energy expenditure in children with cystic fibrosis. J Parenter Enteral Nutr 1999;23:233–6.
[20] Wilson DC, Pencharz PB. Nutrition and cystic fibrosis. Nutrition 1998;14:792–5.
[21] Marchant JM, Masel JP, Dickinson FL, Masters IB, Chang AB. Application of chest high-resolution computer tomography in young children with cystic fibrosis. Pediatr Pulmonol 2001;31:24–9.
[22] Corey M, McLaughlin FJ, Wiliams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 1988;41:583–91.
[23] Schöni MH, Casaulta-Aebischer C. Nutrition and lung function in cystic fibrosis patients (Review). Clin Nutr 2000;19:79–85.