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Resting energy expenditure in cryptogenic fibrosing alveolitis

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ABSTRACT: A proportion of patients with chronic airflow limitation appear to have a raised resting energy expenditure (REE). This has been suggested as the reason for weight loss which may occur in these patients. A previous study found an increased REE in patients with interstitial lung disease of mixed aetiology. We were interested in studying REE in a more homogeneous group, with cryptogenic fibrosing alveolitis (CFA).

Twenty patients with CFA were studied. They were compared with 18 controls matched for age, sex, weight and height. REE was measured by indirect calorimetry. Fat-free mass (FFM), was estimated by anthropometry. Patients had respiratory function tests performed, disability related to breathlessness was assessed by the activity section of the St George's Respiratory Questionnaire.

Mean REE in the CFA group was not different from the control group: 5.20 (0.56) *versus* 5.12 (0.51) kj·h^{-1}·kgFFM^{-1}. REE was elevated to greater than 110% of the value predicted by the Harris-Benedict equation in one CFA patient and in no control subjects. There was no correlation of REE with weight, pulmonary function tests, arterial oxygen saturation or activity score.

The prevalence of a raised resting energy expenditure in cryptogenic fibrosing alveolitis patients with low transfer factor and relatively preserved vital capacity is low, and is less than that reported previously in a group of patients with interstitial lung disease of mixed aetiology.

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A proportion of patients with chronic obstructive pulmonary disease (COPD) or chronic asthma have a raised resting energy expenditure (REE), both when compared to values given by prediction equations and when compared to matched controls [1]. The elevation in REE has been proposed as a possible cause of the weight loss seen in some patients. The mechanism of the elevated REE is not known but it has been proposed that it may, in part, be secondary to an increased work of breathing. If this were the case, patients with other respiratory disorders that caused an increase in the work of breathing would also be expected to have a raised REE. The work of breathing is increased in conditions that cause pulmonary fibrosis [2]. FITTING *et al.* [3] studied 12 patients with interstitial lung disease of mixed aetiology and found their mean REE to be significantly elevated. We were interested in examining the prevalence of hypermetabolism in a more homogenous group of patients with interstitial lung disease, and to see whether there was any relationship between REE and respiratory physiology, body composition and symptom score.

Methods

Patients and study design

Twenty patients with cryptogenic fibrosing alveolitis (CFA) were recruited The diagnosis was made on the basis of a typical history of progressive breathlessness, physical examination revealing bibasal fine inspiratory crackles and finger clubbing, bilateral interstitial shadowing on chest radiography, no coexisting connective tissue disease and no history of exposure to known fibrogenic agents, including asbestos, drugs or other agents known to cause allergic alveolitis. There was no evidence of coexisting cardiac or systemic disease. In addition, the diagnosis was confirmed by transbronchial or open lung biopsy and/or high resolution computed tomography (HRCT) showing typical appearances of basal peripheral lung fibrosis plus areas of ground-glass appearance. Patients with evidence of other disease, particularly emphysema and pleural disease, were excluded. The HRCT scans were all interpreted by one experienced respiratory radiologist.

All patients attending our respiratory out-patients department were screened for possible inclusion and the patients included were sequential patients who met the inclusion criteria, except for one patient who did not want to take part in the study. The patients were studied when they were in a stable clinical state. Respiratory function tests were carried out in a regional lung function laboratory by experienced technicians. Spirometry was measured with a dry wedge spirometer (Vitalograph Ltd, Bucks, UK), lung volumes using a modified water-filled Collins spirometer (Warren E. Collins, MA. USA), and carbon monoxide transfer factor with the adapted Collins spirometer using the single-breath technique. Normal values were taken

from the report of the working party for the European Coal and Steel Community [4]. Arterial blood gas values at rest breathing room air were measured from the radial artery in 14 patients (Radiometer, Copenhagen, Denmark). Eighteen healthy control subjects matched to the patients with regard to age, sex, height and weight were included in this study and underwent the metabolic study and anthropometric measures. The control subjects were matched to the patients with regard to age, sex, height and weight, had never smoked, and had no respiratory symptoms.

REE, body composition, and quality of life

REE was measured by open-circuit indirect calorimetry using a Datex Deltatrac Metabolic Monitor (Datex Instrumentarium Ltd, Helsinki, Finland). This comprises a plastic canopy, which is placed over the head while the subject lies semi-reclined, relaxed and still. Room air is drawn into the canopy by a constant flow-rate generator. The flow-rate is checked monthly by nitrogen gas infusion and remains stable at 42.9 $L \cdot min^{-1}$. A paramagnetic oxygen analyser and an infra-red carbon dioxide analyser sample continuously from the canopy and a microprocessor calculates oxygen consumption ($V'O_2$) and carbon dioxide production ($V'CO_2$). A read out of average values is given at 1 min intervals. Sampling is continued until six steady-state readings (<5% variation) are obtained. This usually takes about 15–20 min. The cumulative variance by this method for $V'O_2$ and $V'CO_2$ in the physiological range as checked by "dummy gases" was <2%. Each time the metabolic monitor was used, the gas analysers were calibrated by means of a commercial calibration gas mixture (Electrochem Ltd, Stoke on Trent, UK), which was independently checked by the Haldane technique.

Measurements were made in the morning after an overnight fast and when the patient was in a stable clinical state. The patients were brought to the laboratory by taxi to minimize exertion that morning. They collected an overnight timed urine sample. On arrival they rested while a quality of life questionnaire, the St George's Respiratory Questionnaire (SGRQ), was administered [5]. REE was measured as described above, and then anthropometric measures were made. These consisted of height, weight, mid-arm circumference (MAC), triceps skinfold (TSF), taken midway between the acromium and the olecranon using skin callipers (John Bull, British Indicators Ltd, Burgess Hill, UK), and handgrip strength (HGS), using a handgrip dynamometer (C.H. Sterling Co., Chicago, USA). A second REE measurement was then made and the results of the two were averaged.

Analysis of variance showed no difference between the first and the second $V'O_2$ and $V'CO_2$ measurement on the same day. Urinary nitrogen was assayed by the Kjheldal technique to give an estimate of nonprotein respiratory quotient using the equations of FRAYN [6]. REE was then estimated and fuel oxidation rates were calculated Muscle mass was estimated from height, TSF and MAC using the equations of HEYMSFIELD *et al*. [7]. Fat mass (FM) was derived from TSF [8] and fat-free mass (FFM) was calculated by subtracting the fat mass from body weight. Although corticosteroid medication can affect distribution of body fat, unpublished work from our unit comparing the use of TSF and dual energy X-ray absorptiometry has shown that this is a valid method of estimating FFM in COPD patients who are taking or have been taking oral corticosteroid medication. REE was expressed as kilojoules per minute ($kJ \cdot min^{-1}$), kilojoules per hour per kilogram of body weight ($kJ \cdot h^{-1} \cdot kg^{-1}$), and as a percentage of the value predicted by the HARRIS and BENEDICT [9] equation (%REEHB). REE was also expressed as kilojoules per hour per kilogram of fat-free mass, ($kJ \cdot h^{-1} \cdot kgFFM^{-1}$) and as a percentage of the predicted value given by the equation of FITTING *et al.* [3], which is related to FFM (%REE-FFM). Ideal body weight, (IBW) was calculated according to the equation of BLAQUE-BELAIR *et al*. [10].

The SGRQ is a validated standardized questionnaire, which gives a score for activity, symptoms and impact, plus an overall score in relation to respiratory disease. It has been used primarily for patients with chronic airflow obstruction but the activity score is relevant for other patients with respiratory dysfunction. Scores are given as a percentage, and a higher score indicates more severe impairment. In our experience, normal controls score 0–11%, therefore we did not measure symptom scores on the control subjects. Further details are given in the Appendix.

The study was approved by the Leeds Eastern Health Authority Clinical Research Ethics Committee.

Data analysis

Data are presented as mean (SD), with 95% confidence intervals (95% CI) given. Differences between groups were analysed using the unpaired two tailed t-test. Statistical significance was taken at the 0.05 level. The relationship between variables was examined using linear regression. It was estimated that the power of the study to detect a difference in REE of 10% was 0.9 (α set at 0.05).

Results

Twenty patients (five females and 15 males) were studied, together with 18 matched controls (five females and 13 males). Fifteen of the patients were receiving maintenance oral prednisolone therapy (mean dose 12.8 mg), of which one in addition was on a regimen of weekly pulsed intravenous methylprednisolone. Seven patients were taking nonsteroidal immunosuppressive therapy (five cyclophosphamide, one azathioprine and one cyclosporine). The mean age of the patients was 62 yrs (range 37–79 yrs). The mean age of the control group was 57 yrs (range 32–71 yrs).

A summary of the respiratory function and SGRQ activity scores of the patients is presented in table 1. Overall, they had relatively well-preserved lung volumes with a mean forced expiratory volume in one second (FEV_1) of 77% predicted and mean total lung capacity (TLC) of 84% pred. However, there was severe impairment of gas exchange, with both the transfer factor of the lung for carbon monoxide ($T_{L,CO}$) and the gas transfer corrected for lung volume (K_{CO}) being less than 45% pred. Most of the patients had high activity scores on the SGRQ, indicating significant restriction of their activity due to breathlessness.

Table 1. – Respiratory function and symptom scores of the subjects studied

FEV_1 % pred	FVC % pred	FEV_1/FVC %	RV/TLC %	VC % pred	TLC % pred	$T_{L,CO}$ % pred	K_{CO} % pred	P_{a,O_2} % pred	SGRQ activity
77±18 (43–119)	86±23 (41–133)	75±13 (54–94)	41±7 (28–61)	85±24 (42–126)	84±17 (52–113)	33±13 (11–65)	40±16 (13–72)	9.5±1.5 (7.3–12.5) n=14	61±21 (17–93)

Data are presented as mean±SD, and range in parenthesis. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; VC: vital capacity; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; P_{a,O_2}: arterial oxygen tension; % pred: percentage of predicted value; SGRQ: St George's Respiratory Questionnaire.

Table 2. – Anthropometric parameters of the subjects studied

Age yrs	Sex M/F	Height m	Weight kg	IBW % pred	FM %	FFM %	FFM kg	HGS kg
Patients								
62±11	15/5	1.67±0.06	76±11	115±15	35±5	65±5	49±7	29±8
Controls								
57±11	13/5	1.68±0.09	74±10	111±11	32±7	68±7	50±7	33±10
(-2.1–12.6)	-	(-0.06–0.04)	(-4.9–9.2)	(-4.8–12.5)	(-1.3–7.0)	(-7.0–1.3)	(-5.5–3.8)	(-9.8–2.6)

Data are presented as mean±SD, and 95% confidence interval for the difference in parenthesis. IBW: ideal body weight; FM: fat mass; FFM: fat-free mass; HGS: hand grip strength (dominant side); M: male; F: female; % pred: percentage of predicted value.

Table 3. – Resting energy expenditure (REE) of the subjects studied

REE				
$kJ \cdot min^{-1}$	$kJ \cdot hr^{-1} \cdot kgBW^{-1}$	% predHB	$kJ \cdot h^{-1} \cdot kgFFM^{-1}$	% predFFM
Patients				
4.24±0.63	3.39±0.43	98±10	5.20±0.56	104±12
Controls				
4.24±0.60	3.47±0.31	97±6	5.12±0.51	102±9
(-0.40–0.40)	(-0.32–0.17)	(-4.2–7.0)	(-0.28–0.43)	(-4.4–9.6)

Data are presented as mean±SD, and 95% confidence interval for the difference in parenthesis. BW: body weight; % predHB: percentage predicted by the equation of HARRIS and BENEDICT [9]; FFM: fat-free mass; % predFFM: percentage predicted by fat-free mass using the equation of FITTING *et al*. [3].

Body composition

The patients were well-matched with controls for weight and height, as is shown in table 2. The mean (SD) weight of patients was 115 (15)% of IBW. One patient was significantly underweight, at less than 90% IBW. Mean (SD) muscle mass estimated from TSF and MAC was 29.9 (4.3) kg in the CFA patients and 31.9 (7.0) kg in the controls (difference nonsignificant (NS)). There was a very strong correlation between the muscle mass estimated from the TSF and MAC and FFM estimated by TSF according to the equation of DURNIN and WORMERSLEY [8] ($p<0.0001$, Pearson's correlation coefficient). FM and FFM were present in similar proportions in patients and controls. HGS was similar in both groups.

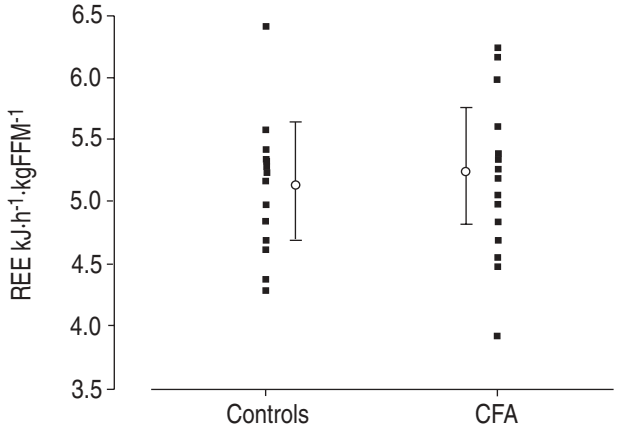

Fig. 1. – Resting energy expenditure (REE) of patients with cryptogenic fibrosing alveolitis (CFA) and control subjects. FFM: fat-free mass. Open symbols and bars indicate mean±SD.

REE

There was no significant difference in REE between the patient and control group, as shown in table 3 and figure 1. The mean (SD) REE of the CFA patients was 98 (10)% of the value predicted by the Harris Benedict equation, and only one patient had a REE significantly higher than expected, at 111%. For the control group, mean (SD) REE was 97 (6)% (95% CI for the difference, -4–7%). REE expressed per kilogram of FFM was 5.20 (0.56) $kJ \cdot h^{-1} \cdot kgFFM^{-1}$ in the patients, and 5.12 (0.51) $kJ \cdot h^{-1} \cdot kgFFM^{-1}$ in the controls (95% CI for the difference -0.28–0.43). The equation of FITTING *et al*. [3] was used for estimation of predicted REE per kilogram FFM based on 46 normal male subjects; and it was found that %REEFFM of the CFA patients was 104 (12)% predicted and for controls was 102 (9)%, (95% CI -4.4–9.6%) (fig. 2). There was no correlation between REE and %FFM, $T_{L,CO}$, vital

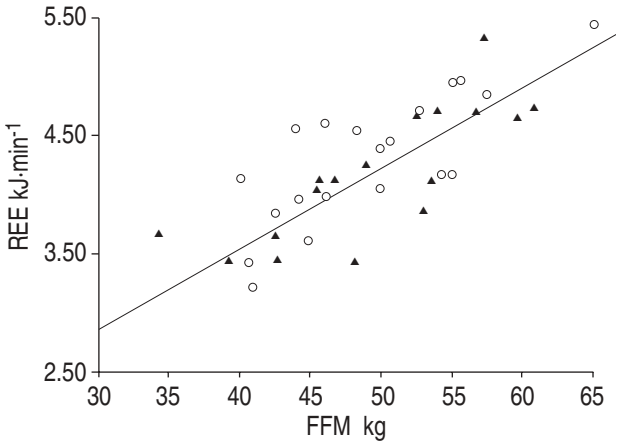

Fig. 2. – Resting energy expenditure (REE) related to fat-free mass (FFM) in patients with cryptogenic fibrosing alveolitis (○) and in controls (▲). ——— : Fitting's regression [3].

capacity (VC), arterial oxygen tension (P_{a,O_2}) or activity scores. The mean (SD) nonprotein respiratory quotient was 0.82 (0.05) in patients and 0.81 (0.06) in controls, and there was no significant difference in the pattern of fuel oxidation between the patients and controls (patients: glucose 33%, fat 50%, protein 17%; controls: glucose 38%, fat 46%, protein 16%).

Discussion

Our results differ from those of FITTING *et al.* [3], who found that in a group of 12 patients with interstitial lung disease of mixed aetiology mean REE was elevated, at 118.8% of that predicted by the Harris-Benedict equation. There are, however, marked differences between these two sets of patients. The present group all had CFA, as defined above, whilst the group studied by FITTING *et al.* [3] had diseases of mixed aetiology, including sarcoidosis, silicosis, histiocytosis X and hypersensitivity pneumonitis. The pattern of physiological impairment was also different; overall the group studied by FITTING *et al.* [3] had severe restriction of VC, with relatively well-preserved $T_{L,CO}$ and K_{CO}, whilst this situation was reversed in the present patients. However, within the group studied by FITTING *et al.* [3] there was variable physiology, and we would suggest that it is difficult to generalize when this is the case. Another explanation for the different findings is that some of the patients studied by FITTING *et al.* [3] may have been at a later stage of their disease, though this was not the case in all. The patients in the present study certainly had severe disease, as judged by the severity in impairment in $T_{L,CO}$, hypoxia, and very reduced activity levels on the SGRQ.

FITTING *et al.* [3] interpreted their results as lending support to the hypothesis that elevation of REE is related to the increased work of breathing. Another hypothesis is that their patients may have had disease processes with a greater degree of active inflammation associated with an increase in circulating cytokines, which raise the metabolic rate. Recent work has shown an association with tumour necrosis factor (TNF) and elevated REE in COPD [11], but cytokine levels were not measured in either the present study or that of FITTING *et al.* [3]. Eight out of the 12 patients studied by Fitting probably had high levels of inflammation, as judged by the diagnosis given. The work of breathing was not measured in either study. Most previous studies measuring work of breathing have done so when a stress was put on the respiratory system. Although this may show that work increases disproportionately in respiratory disease, this cannot be extrapolated to definitely infer that work is increased in the basal state. LOURENÇO *et al.* [2] also found elevation of V'_{O_2} in a group of patients with mixed interstitial disease, but V'_{O_2} was measured using a mouthpiece system, which has been shown to overestimate V'_{O_2} compared to canopy methods.

Five of the patients studied by FITTING *et al.* [3] showed evidence of nutritional depletion, with weight <90% IBW predicted, whereas the present group, as a whole, were overweight. Only one of the present patients was significantly underweight (<90% IBW). Interestingly, the mean absolute weight of FFM in these patients was practically identical to those of FITTING e*t al.* [3] at 48.6 *versus* 47.7 kg. This implies that the difference in weight between the two groups is primarily due to differences in FM, and may be explained by loss of FM in the patients of FITTING *et al.* [3] (with relative preservation of muscle mass), and/or gain primarily of FM in the present patients. The differences in body composition may well be due to corticosteroid medication (although there was no significant difference in percentage FM between the present patients and controls). At the time of the study, 15 out of 20 of the present patients were taking oral corticosteroids, compared to six out of 12 of the group studied by FITTING *et al.* [3]; and possibly the present patients had been taking corticosteroids for a longer period of time.

We found no relationship between REE and any measure of disease severity. FITTING *et al.* [3] found a correlation between REE and alveolar-arterial pressure difference for oxygen ($P_{(A\text{-}a),O_2}$), which we did not. Interestingly, the one patient who was hypermetabolic as judged by the Harris-Benedict equation was the patient most severely affected by her disease in terms of reduced VC, quality of life and clinical assessment. However, she was also the smallest patient, and it is possible that prediction equations consistently underestimated metabolic rate in underweight subjects (we have found it practically impossible to find matched controls for very thin people). This underestimation of metabolic rate could be explained, in part, by the relative increase in FFM with decreasing body weight, particularly when weight loss has occurred, as FFM is, at present, the best indicator of metabolically-active tissue.

In conclusion, we found a low prevalence of elevation of resting energy expenditure in a group of well-nourished patients with cryptogenic fibrosing alveolitis with severe impairment of gas transfer and preserved lung volumes. Before it can be concluded that metabolic rate is raised in patients with other interstitial lung diseases, further studies in particular disease categories are required.

Appendix

Activity Section of St George's Respiratory Questionnaire

This consists of seven activities that may make a person feel breathless and nine activities that may be affected by

a person's breathing. The respondent is required to give a positive response if affected. The questions are weighted and the score is expressed as a percentage, with high scores indicating greater disability. Examples of representative scores are given below:

Usually breathless when sitting or lying still and takes a long time to get washed or dressed=100%

Breathless walking around the home and finds that jobs such as housework take a long time=72%

Breathless after walking up a flight of stairs and has to stop or slow down if hurries or walks fast=41%

Breathless walking up hills and finds light gardening, dancing, playing bowls difficult due to breathing=29%

Only really becomes breathless playing sports or games and would find it difficult to run, cycle or swim fast=11%

(In our experience, normal subjects score 0–11%)

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