

Resting energy expenditure and oxygen cost of breathing in patients with cystic fibrosis

S C Bell, M J Saunders, J S Elborn, D J Shale

Abstract

Background – Resting energy expenditure (REE) is often increased and may contribute towards energy imbalance in patients with cystic fibrosis. Several mechanisms may lead to increased REE including the gene defect, the effect of chronic infection, and abnormal pulmonary mechanics. Increased oxygen cost of breathing (OCB) has been demonstrated in patients with chronic obstructive pulmonary disease (COPD), but has not been the subject of extensive study in cystic fibrosis.

Methods – Ten clinically stable patients with cystic fibrosis and 10 healthy control subjects were studied. OCB was estimated using the dead space hyperventilation method. Mixed expired gas fractions were measured by online gas analysers and ventilation by a pneumotachograph. After measurement of resting ventilation and gas exchange, minute ventilation (\dot{V}_E) was stimulated by 6–10 l/min by the addition of a dead space and OCB calculated from the slope of the differences in oxygen uptake (\dot{V}_{O_2}) and \dot{V}_E . REE and the non-respiratory component of REE were calculated from gas exchange data. To assess the repeatability of OCB all subjects had a further study performed one week later.

Results – The patients had lower weight, fat free mass (FFM), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and transfer factor for carbon monoxide (TLCO) than controls. Resting respiratory rate, \dot{V}_E , and oxygen uptake per kilogram of FFM ($\dot{V}_{O_2}/\text{kg FFM}$) were higher in patients (20 (7), 10.4 (1.4) l/min and 5.5 (0.8) ml/kg FFM/min) than in controls (13 (4), 7.0 (1.2), and 4.2 (0.5), respectively.) The error standard deviation for replicate measures of OCB was 0.5 ml O_2 /l \dot{V}_E in controls and 0.8 ml O_2 /l \dot{V}_E in patients with coefficients of variation of 24% in controls and 28% in patients. The mean OCB in patients was 2.9 (1.4) ml O_2 /l \dot{V}_E and 2.1 (0.7) ml O_2 /l \dot{V}_E in controls. OCB, expressed as ml/min ($\dot{V}_{O_2}/\text{resp}$) was 28.5 (11.7) in patients and 14.0 (3.6) in controls. REE was higher in patients (125.9 (14.0)% predicted) than in controls (99.0 (9.4)%). The estimated non-respiratory component of REE was 112.1 (14.9)% for patients and 93.0 (10.0)% for controls.

Conclusions – In clinically stable patients with cystic fibrosis the OCB at rest is in-

creased but is not the sole explanation for increased metabolic rate. This contrasts with the finding in COPD where the increase in REE is largely explained by increased OCB. This study also showed poor repeatability and OCB measurements similar to earlier studies, which indicates that the technique is not suitable for longitudinal studies.

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Keywords: cystic fibrosis, resting energy expenditure, oxygen cost of breathing.

Low body weight is common in cystic fibrosis and is related to inadequate energy intake, nutrient malabsorption, and excessive energy expenditure. Resting energy expenditure (REE), an estimate of basal metabolic rate, is 10–20% greater than in healthy subjects and may contribute to energy imbalance.^{1,2}

At least three mechanisms – the gene defect, the consequences of chronic pulmonary infection, and altered lung mechanics – could contribute to increased basal metabolic rate in cystic fibrosis. Cultured epithelial and connective tissue cell lines with a cystic fibrosis genotype have greater oxygen demands than non-cystic fibrosis cells.^{3,4} The increased energy expenditure in infants with cystic fibrosis may be related to the gene defect, but there is conflicting evidence relating the raised REE to genotype and lung disease.^{2,5,6}

The cystic fibrosis genotype is unlikely to account for all the increase of REE in patients with established lung disease, particularly that characterised by chronic bacterial infection and an intense inflammatory response associated with airways and parenchymal damage. Bronchial sepsis leads to local release of leukotrienes, free oxygen radicals, and cytokines including tumour necrosis factor alpha (TNF α) and the interleukins IL-1 β and IL-8.^{7–10} Circulating TNF α levels in patients with cystic fibrosis and chronic pulmonary infection have been associated with an increased REE.¹¹

Continuous injury to the lungs leads to progressive parenchymal fibrosis and airway obstruction resulting in abnormal lung mechanics with probable increased oxygen cost and work of breathing. This is supported by the inverse relationship between increased REE and the severity of airways obstruction in cystic fibrosis.^{1,12} Increased oxygen consumption by respiratory muscles occurs in chronic ob-

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structive pulmonary disease (COPD) and this might account for the increase in REE.^{13 15 16}

In view of the limited published data on oxygen cost of breathing (OCB) in cystic fibrosis, we sought to determine whether the OCB was increased in clinically stable patients and its contribution to the increase in REE in patients with cystic fibrosis. We also examined the repeatability of the measurement of OCB in patients and healthy volunteers.

Methods

SUBJECTS

Ten adult patients with cystic fibrosis diagnosed in childhood (sweat levels of sodium and chloride >70 mmol/l) and 10 age and sex matched healthy volunteers were studied. The number of subjects studied was based on a power calculation of data from a study of patients with COPD using similar methods and experimental protocol.¹⁶ The difference in OCB between patients and controls was 2.1 ml oxygen/litre of ventilation (ml O₂/l $\dot{V}E$) with a standard deviation of 1.3 ml O₂/l $\dot{V}E$ in patients. The estimated numbers in each group to detect a significant difference ($p < 0.05$) with a power of 90% were 8.2 (that is, nine subjects per group). Patients were studied during a period of clinical stability, defined as no change in symptoms or treatment in the month preceding study and a forced expiratory volume in one second (FEV₁) within 10% of the best recorded in the previous 12 months. All had chronic infection with *Pseudomonas aeruginosa* but no evidence of co-existent diabetes mellitus or liver disease. One patient was prescribed long term nocturnal oxygen but this was stopped two hours before arrival for the study.

Written informed consent was obtained from subjects and the study was approved by the local ethics research committee.

STUDY DESIGN

Patients and volunteers were admitted from home following a 12 hour fast and acclimatised to the study environment in a comfortable chair for 60 minutes whilst listening to music. During this period all subjects had a short trial of mouthpiece breathing to familiarise them with the apparatus and protocol. Usual medications included pancreatic replacement enzymes and fat soluble vitamins ($n = 10$), inhaled β_2 agonists ($n = 5$), inhaled corticosteroids ($n = 2$), prophylactic antibiotics ($n = 7$), and the oral contraceptive pill ($n = 1$). Patients had their morning medication withheld and had no β_2 agonist bronchodilators in the 12 hours prior to study. The oral contraceptive pill was the only medication in volunteers ($n = 3$).

The OCB was measured using a modification of the technique originally described by Liljestrand.¹⁷ Studies were performed on two mornings, 7–10 days apart, at a controlled temperature (21–24°C), under identical conditions of preparation and protocol. Subjects breathed through a low resistance one way valve system (dead space 75 ml). Inspired volume was measured by digital integration of the

flow signal obtained from a pneumotachograph (GM Instruments, Scotland) and a micromanometer (Furness Controls Ltd, Sussex, UK). Expired gas passed into a mixing chamber (3000 ml) with continuous gas sampling into an infrared CO₂ analyser and paramagnetic O₂ analyser (PK Morgan, Kent, UK). The electrical output from the micromanometer was sampled 30 times/second by an Acorn 3100 computer. The gas analysers were calibrated prior to each series of measurements using alpha-gravimetrically prepared gas mixtures (BOC, UK) and had linear responses within the physiological range. The pneumotachograph was calibrated using a one litre syringe and had a linear response between 2 and 20 l/min.

Respiratory gas exchange was monitored for 15 minutes. Steady state ventilation was defined when the subject reached a stable $\dot{V}E$ (± 1 l/min). This was achieved within five minutes in all cases. The initial five minutes of data were discarded and data from the subsequent 10 minutes were used for calculation of mean minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) using standard equations. After resting for a further 15 minutes hyperventilation was induced by the addition of a dead space of known volume between the mouthpiece and one way valve assembly to increase minute ventilation by 5–10 litres, and gas exchange and $\dot{V}E$ were measured as above. A pilot study suggested a dead space volume of two thirds of tidal volume in controls and one half of tidal volume in patients were required to increase ventilation. Resistance in the breathing circuit, including the largest dead space, was < 0.5 cm H₂O l⁻¹ s⁻¹ at a flow rate of 100 l/min.

Ethanol combustion and nitrogen dilution methods used to validate ventilated hood systems are not feasible to validate gas exchange measurement using the system described above, so comparison of resting $\dot{V}O_2$ was made with a ventilated hood indirect calorimeter.¹⁸ Subjects were transferred to the metabolic investigation room by wheelchair immediately following estimation of OCB on the first study day. After acclimatisation gas exchange was monitored for 20 minutes in the ventilated hood. Although comparison between systems is not a true validation of respiratory gas exchange using the mouthpiece, the ventilated hood measurements were made to verify independently that overall measurements of $\dot{V}O_2$ were similar.

Pulmonary function tests were performed on all subjects on day 1 including flow volume curves, lung volumes by helium dilution, and transfer factor by the single breath carbon monoxide method (Transfer Test USA, PK Morgan, Kent, UK). The predicted normal values used for spirometric testing were those of Knudsen, for lung volumes those of Polgar (<20 years) and Goldman (>20 years), and for transfer factor those of Cotes.^{19–22} Spirometric tests were performed and serum C reactive protein (CRP) was collected on both days of the study.

Height was recorded using a stadiometer and weight using a balance beam scale (accurate to 0.1 kg). Body mass index was calculated as weight/height² (kg/m²). Fat free mass was estimated by measurement of four skin folds using calipers (Holtain, UK) and the equations of Durnin and Womersley.²³

FORMULAE AND CALCULATIONS

Oxygen cost of breathing (ml O₂/l $\dot{V}E$) was calculated from data collected on each visit by:

$$\frac{[\text{Dead space } \dot{V}O_2 - \text{Resting } \dot{V}O_2]}{[\text{Dead space } \dot{V}E - \text{Resting } \dot{V}E]}$$

Mean data from both study days was calculated for each individual for $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and OCB.

Resting energy expenditure was calculated using the equation of Weir²⁴:

$$\text{REE (kJ/day)} = [(3.941 \times \dot{V}O_2) + (1.10 \times \text{RER} \times \dot{V}O_2)] \times 6.025$$

Oxygen consumption of the respiratory muscles ($\dot{V}O_{2\text{resp}}$) was estimated using the equation:

$$\dot{V}O_{2\text{resp}} \text{ (ml/min)} = \text{O}_2\text{cost (ml/l } \dot{V}E) \times \text{resting minute ventilation (}\dot{V}E)$$

The non-respiratory energy expenditure was estimated by:

$$\dot{V}O_{2\text{non-resp}} = \dot{V}O_{2\text{total}} - \dot{V}O_{2\text{resp}}$$

and

$$\text{REEnon-resp (kJ/day)} = [(3.941 \times \dot{V}O_{2\text{non-resp}}) + (1.10 \times \text{RER} \times \dot{V}O_2)] \times 6.025$$

Predicted REE was determined using the equations of Harris-Benedict.²⁵

STATISTICAL ANALYSIS

Comparison between groups was made using unpaired *t* tests and the Mann-Whitney test was applied to data not normally distributed. Mean data from both study days were calculated for each individual for respiratory gas exchange, ventilation, and OCB measurements. Linear regression analysis was performed to analyse the relationship between

OCB and forced expiratory volume in one second (FEV₁), transfer factor for carbon monoxide (TLCO) and residual volume to total lung capacity ratio (RV/TLC). Repeatability of OCB was assessed according to the method of Bland and Altman by calculation of the error standard deviation of repeatability and coefficient of variation (CV%).²⁶ A value of *p*<0.05 was considered to be statistically significant. Analysis was performed using Unistat v 2.0 (London, UK).

Results

Patients had lower weight and BMI than control subjects and FEV₁ and forced vital capacity (FVC) were less in the patient group. Patients with cystic fibrosis had a greater residual volume and reduced TLCO than healthy controls. Total lung capacity tended to be lower but the difference compared with controls was not significant (table 1). The mean (SD) serum CRP concentration was 29.3 (26.4) mg/l in patients, significantly higher than 2.2 (1.7) mg/l in controls (*p*<0.0001).

Resting $\dot{V}O_2$, measured from the mouthpiece and nose clip system, was not different from resting $\dot{V}O_2$ determined by the ventilated hood indirect calorimeter method. The mean difference (95% CI) in resting $\dot{V}O_2$ (mouthpiece-hood system) was 2.7 (−9.8 to 15.1) ml/min in controls and 9.4 (−2.5 to 21.3) ml/min in patients. Resting $\dot{V}O_2$ using the mouthpiece was greater in five controls and six patients than for the ventilated hood.

REPEATABILITY

The FEV₁, FVC, and serum CRP concentration did not change significantly between study days. There was no difference in OCB between study days in either group. The error standard deviation for repeated measures for OCB was 0.5 ml O₂/l $\dot{V}E$ in controls and 0.8 ml O₂/l $\dot{V}E$ in patients. This is a large proportion of the mean OCB of 2.1 ml O₂/l $\dot{V}E$ and 2.9 ml O₂/l $\dot{V}E$ in controls and patients, respectively, and is reflected in the coefficient of variation (CV%) for OCB in controls (24%) and in patients (28%). The CV% for $\Delta\dot{V}O_2$ (dead space – resting) between the two study days was 27% in controls and 35% in patients, and for $\Delta\dot{V}E$ was 10% and 17%, respectively.

Table 1 Mean (SD) anthropometric and lung function data

	Cystic fibrosis	Normal subjects	Mean difference (95% CI)
Sex (M/F)	6/4	6/4	—
Age (years)	22.4 (3.7)	24.0 (4.5)	−1.6 (−5.2 to 2.5)
Weight (kg)	56.5 (8.2)	69.0 (10.3)	−12.5 (−21.3 to −3.7)‡
Height (m)	1.66 (0.06)	1.73 (0.09)	−0.07 (−0.14 to 0.01)
BMI (kg/m ²)	19.6 (2.3)	22.5 (2.1)	−2.9 (−4.3 to −0.9)*
FFM (kg)	48.9 (8.2)	57.2 (12.2)	−8.3 (−18.1 to 1.6)
Fat (%)	13.5 (5.4)	17.6 (7.0)	−4.1 (−10.0 to 1.8)
FEV ₁ (% pred)	40.0 (18.1)	108 (7.4)	−68.1 (−54.6 to −18.5)†
FVC (% pred)	56.7 (22.9)	108 (10.5)	−54.5 (−68.7 to −34.2)†
TLco (% pred)	68.9 (26.2)	91.7 (9.5)	−22.8 (−42.1 to −3.5)*
TLC (% pred)	83.4 (23.4)	100 (8.6)	−16.7 (−34.0 to 0.6)
RV (% pred)	138 (63.3)	84.4 (16.6)	53.3 (7.3 to 99.3)*

BMI = body mass index; FFM = fat free mass; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; TLco = lung transfer factor for carbon monoxide; TLC = total lung capacity; RV = residual volume.

* *p*<0.05; † *p*<0.01; ‡ *p*<0.001.

Table 2 Mean (SD) resting respiratory gas exchange and ventilation

	Cystic fibrosis		Normal subjects		Mean difference (95% CI)	
RR (breaths/min)	20	(7)	13	(4)	7	(0 to 12)*
VE (l/min)	10.4	(1.4)	7.0	(1.2)	3.8	(2.2 to 4.8)**
VO ₂ (ml/min)	266.1	(30.8)	237.2	(44.3)	35.0	(-5.5 to 73.2)
VO ₂ (ml/kg FFM/min)	5.5	(0.8)	4.2	(0.5)	1.3	(0.7 to 2.0)**
RER	0.77	(0.04)	0.80	(0.05)	-0.03	(-0.07 to 0.02)
REE (kJ/min)	5.4	(0.6)	4.8	(0.9)	0.7	(-0.1 to 1.5)
REE (kJ/kg FFM/min)	0.112	(0.02)	0.085	(0.01)	0.027	(0.01 to 0.04)**

RR=respiratory rate; VE=minute ventilation; VO₂=oxygen uptake; RER=respiratory exchange ratio; REE=resting energy expenditure.

* p<0.05; ** p<0.001.

Table 3 Oxygen uptake, minute ventilation, and oxygen cost of breathing in controls and patients with cystic fibrosis

	VO ₂ rest (ml/min)		VE (l/min)		ΔVE (l/min)		O ₂ cost (ml O ₂ /l VE)	
	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
Control subjects								
1	279.9	293.4	5.4	5.9	4.5	4.0	2.9	1.9
2	274.4	285.8	7.4	6.8	6.1	6.7	1.3	1.8
3	205.3	205.3	6.8	7.0	5.3	5.4	2.2	3.9
4	216.4	242.8	8.2	9.6	8.5	8.6	1.4	0.9
5	213.7	203.4	7.4	6.6	6.4	6.7	2.2	3.0
6	240.6	254.4	6.8	7.5	5.8	5.6	1.6	1.9
7	201.5	187.3	7.0	6.3	6.2	6.5	2.7	2.1
8	291.2	345.9	8.4	9.4	8.8	6.4	1.5	1.6
9	176.4	201.3	5.1	5.4	7.5	6.6	2.6	2.8
10	204.7	220.1	6.2	6.4	5.4	6.0	1.3	1.7
Mean (SD)	230.4 (39.0)	244.0 (51.0)	6.9 (1.1)	7.1 (1.4)	6.5 (1.4)	6.3 (1.2)	2.0 (0.6)	2.3 (0.9)
Cystic fibrosis subjects								
1	255.8	263.0	10.8	11.4	6.8	8.9	0.9	0.5
2	250.7	245.5	13.1	10.6	10.5	14.6	2.1	1.0
3	274.6	296.6	8.2	9.8	8.9	9.0	2.0	2.0
4	267.5	275.2	11.6	10.9	7.8	8.8	4.2	1.9
5	192.5	255.7	7.2	9.3	5.5	8.2	5.4	3.5
6	268.1	296.3	8.6	8.6	5.8	7.5	3.4	4.7
7	300.6	309.4	10.9	12.0	9.2	8.4	1.3	2.7
8	280.9	309.9	11.0	12.1	5.9	7.0	3.2	2.9
9	271.6	288.2	10.8	12.6	8.7	10.7	2.4	2.6
10	214.0	205.1	9.9	9.1	5.7	5.9	4.8	4.9
Mean (SD)	257.6 (19.6)	274.5 (20.8)	10.2 (1.8)	10.6 (1.4)	7.5 (1.8)	8.9 (2.4)	3.0 (1.5)	2.7 (1.4)

VE=minute ventilation; VO₂=oxygen uptake.

OXYGEN COST OF BREATHING AND REE

Mean resting VO₂ was greater in patients than healthy subjects when expressed per kilogram of fat free mass. Resting VE and respiratory rate (RR) were also greater in the patient group but respiratory exchange ratio (RER) was not different from control subjects (table 2). The volume of dead space required to induce hyper-

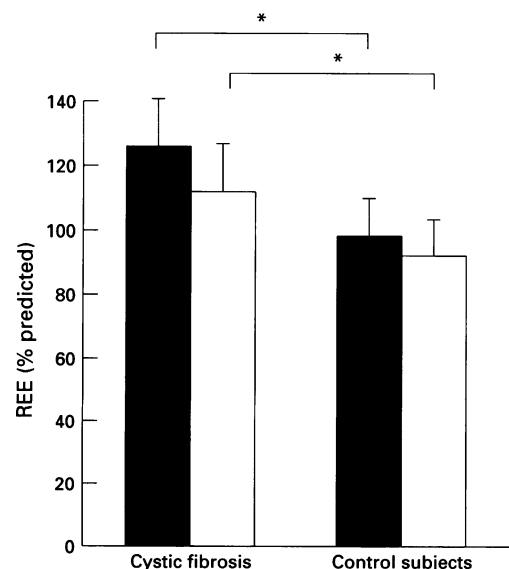
ventilation was similar in both groups (380 (80) ml in controls and 330 (125) ml in patients). Dead space increased ventilation by 6.4 (1.2) l/min in control subjects and 8.2 (2.0) l/min in patients (p<0.05).

The mean OCB in patients was 2.9 (1.4) ml O₂/l VE and tended to be greater than in the control group 2.1 (0.7) ml O₂/l VE (p=0.15) (table 3). Oxygen cost, expressed in ml/min, was greater in patients (28.5 (11.7)) than in controls (14.0 (3.6)) (p<0.001). In patients multiple linear regression analysis did not reveal a significant relationship (r²=0.39, F=1.3) between OCB and FEV₁% predicted, TLC₀% predicted, or the RV/TLC ratio.

Resting energy expenditure, expressed as a proportion of Harris-Benedict equations, was greater in patients (125.9 (14.0)%) than in controls (99.0 (9.4)%) (p<0.001). Although OCB was greater in patients with cystic fibrosis, the estimated non-respiratory component of REE (REE_{non-resp}/REE_{pred}) was 112.1 (14.9)% in patients which was greater than that for healthy volunteers (93.0 (10.0)%) (p<0.001) (figure).

Discussion

The OCB at rest was greater in patients with cystic fibrosis than in healthy control subjects studied under identical conditions. This supports and extends an earlier study where two of three subjects with cystic fibrosis had a raised



Mean (SD) total (■) and non-respiratory (□) resting energy expenditure (REE) in patients with cystic fibrosis and control subjects. * p<0.0001.

OCB compared with control subjects, though comparisons are difficult because of the small numbers involved and differences in techniques used.²⁷ The values for OCB in the healthy controls in this study are similar to those reported by others.^{16,28-30} Many studies have estimated OCB in patients with COPD. The mean OCB in patients with cystic fibrosis was less than that reported in COPD using similar methods, though the range of OCB is greater in COPD (1.0–6.1 ml O₂/l VE,¹⁶ 1.7–18.5,²⁸ and 4.7–8.2³⁰). Although the pathogenesis differs between COPD and cystic fibrosis, there are similarities resulting in raised REE and poor maintenance of body mass.

The lack of an inverse relationship between OCB and pulmonary function tests in our patients was surprising. In two populations of patients with COPD spirometric parameters, resting ventilation, and OCB in the well nourished group were similar to the patients with cystic fibrosis in this study with an OCB of 2.6 (1.1) ml O₂/l VE. In the undernourished patients with more severe pulmonary disease the oxygen cost was greater at 4.3 (1.0) ml O₂/l VE.¹⁶ In patients with COPD negative correlations between FEV₁ and oxygen cost have been found in some studies.³⁰ The failure to demonstrate the expected relationship between OCB and pulmonary function tests, as an index of the severity of lung disease, may relate to variability of the measurement of OCB in the small population studied here. A further factor may be the wide variation in severity of airways limitation and gas trapping in this population as evidenced by the standard deviations for FEV₁ and residual volume.

In many studies OCB has been estimated by stimulating ventilation with an increased dead space, an increased inspiratory resistance, or by CO₂ induced hyperventilation.^{13,14,27,30} Irrespective of the method, determination of oxygen cost assumes a linear relationship between V_{O₂} and VE within the range of ventilation studied. A linear relationship is maintained to at least 30 l/min in healthy subjects to 20 l/min in patients with COPD.¹⁵ We therefore aimed to maintain the increase in ventilation below 20 l/min, and the mean increase in our patients was 8.0 l/min which is similar to the level in studies of patients with COPD in which OCB was estimated.^{13,16,30}

The most important technical issue with the measurement of the OCB is the repeatability of the method which limits the value of this technique in longitudinal studies. The error standard deviation for repeated measurement of OCB in both control subjects and patients was a significant proportion of the mean OCB. This is similar to the between day repeatability in patients with COPD where an average difference of 0.9 ml O₂/l VE was reported.¹⁶ Two factors may account for such variability. Augmented ventilation causes a proportionately smaller increase in V_{O₂} than VE. Day to day differences in the ΔV_{O₂} therefore had a greater effect on the calculation of oxygen cost than ΔVE. Relatively small differences in measurement of V_{O₂} at rest and/or during dead space ventilation may be magnified in the cal-

ulation of the OCB. During hyperventilation the difference between F_{IO₂} and F_{EO₂} is reduced, which may result in measurement error of gas concentration within the oxygen analyser. Despite careful preparation of subjects, the coefficient of variation was in excess of 20% which is similar to values reported previously. Donahoe reported repeatability in patients (but not controls) for studies performed on consecutive days. The average day to day difference was 0.9 ml O₂/l VE of a mean OCB of 3.4, giving an approximate CV of 27%.¹⁶ In the only previous study of OCB in cystic fibrosis the mean CV for controls (n=3) was 31% and for patients (n=3) was 32%.²⁷

Increased OCB reflects abnormal pulmonary mechanics and structure, and has been suggested as a factor in the excessive energy expenditure associated with chronic pulmonary injury in cystic fibrosis. Accepting the limitations imposed by the methodology used in this study, OCB accounted for less than 50% of the additional REE. This is supported by the weak relationship between spirometric values and REE, which suggests that additional factors to abnormal pulmonary mechanics contribute to increased REE.^{11,12} This is in contrast to the situation in patients with COPD where the increase in REE was largely accounted for by increased OCB.¹⁶ However, we have previously shown that one third of the variance of REE is explained by circulating TNFα concentrations and a further one third by FEV₁, which suggests that the host inflammatory response may influence energy expenditure in chronically infected patients with cystic fibrosis.¹¹

Chronic bronchial infection is associated with local production of cytokines, including TNFα, IL-1β and IL-8.^{9,10} Infusion of TNFα in healthy volunteers induces an acute increase in REE with pyrexia, proteolysis, lipolysis, and release of acute phase proteins.³¹ Immunoreactive circulating TNFα has been detected in clinically stable patients with cystic fibrosis, though its biological significance remains uncertain.³²

A further factor may be the effect of the abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein on REE. In vitro studies suggest that the genetic defect may increase oxygen consumption, and both REE and total energy expenditure may be increased in infants with cystic fibrosis.^{4,5} However, interpretation of these findings is complicated by difficulties in estimating severity of lung disease and excluding intercurrent infection in infants. Additionally, patients homozygous for the ΔF508 mutation have higher REE than heterozygotes and non-ΔF508 patients, but the homozygote group has more severe lung disease which may have an independent influence on increased REE.² In contrast, a study of well nourished men with mild bronchiectasis showed that genotype did not have a major effect on REE in patients with cystic fibrosis.⁶

In clinically stable patients with cystic fibrosis the OCB at rest is increased compared with healthy volunteers, but the increased OCB was

not the sole cause of the increased REE observed in our patients. The lack of repeatability severely limits the use of OCB, measured by current methods, in longitudinal studies of chronic progressive lung disorders.

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