Resting energy expenditure and substrate oxidation rates in cystic fibrosis

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Abstract

The resting energy expenditure (REE) and substrate oxidation rates in 16 patients with cystic fibrosis who had mild chest disease and 11 healthy controls were measured using indirect calorimetry. The mean REE (% predicted) in the patients with cystic fibrosis was 11% greater than in the controls. Five patients with cystic fibrosis were hypermetabolic but only one of these had a clinically significant reduction of respiratory function. A greater proportion of REE was derived from carbohydrate oxidation in the cystic fibrosis patients (43.5% v 29.9%). However, the 24 hour dietary intake of carbohydrate was greater in the cystic fibrosis group (49.6 v 45.8% of energy intake).

These data suggest that a high dietary intake of carbohydrate may contribute to the increased oxidation of carbohydrate in these cystic fibrosis patients. All patients with cystic fibrosis, including those with apparently mild lung disease, should continue to receive a high energy diet.

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The importance of a good nutritional state in cystic fibrosis is generally accepted.^{1,2} However, anorexia and a poor energy intake, malabsorption, and an increased energy expenditure are adverse factors that must be overcome to achieve this.

Resting energy expenditure (REE) or resting metabolic rate is raised in cystic fibrosis,³⁻⁵ but there is disagreement as to whether total daily energy expenditure is increased.^{6,7} A specific energy consuming defect in cystic fibrosis has been proposed,^{4,6} particularly in those carrying the $\delta F508$ mutation,⁸ although this is questioned.⁹

The bases of nutritional management in cystic fibrosis are the provision of a high energy diet without restriction of dietary fat,^{10,11} the reduction of faecal energy losses through adequate pancreatic enzyme replacement treatment, and aggressive antibiotic treatment of the chest infection. However, even with this approach some patients with cystic fibrosis are poorly nourished. More intensive efforts at nutritional rehabilitation by nasogastric or gastrostomy feeding may result in weight gain, but this is predominantly an increase in body fat mass relative to lean body mass.^{12,13} In view of these difficulties, knowledge of the fate of dietary substrates in patients with cystic fibrosis would seem to be of relevance.

A raised respiratory quotient in patients with cystic fibrosis has been observed, suggesting an increased contribution of carbohydrate oxidation to energy metabolism.^{5,7,8} However, only

one study considered the effect of dietary intake on substrate oxidation and no relationship was found.⁸

The aim of the present study was to determine the REE and substrate oxidation rates in cystic fibrosis and to relate these to the severity of the disease state, the genetic status, and the dietary intake.

Patients

Sixteen patients with cystic fibrosis (six males, 10 females; mean age 13.3 years, range 10.5 to 23.5 years) from the Leeds cystic fibrosis clinic were studied. All had classical features compatible with cystic fibrosis and sweat sodium and chloride concentrations greater than 60 mmol/l.¹⁴ The subjects had mild chest disease, no clinical or biochemical evidence of liver disease, and no recorded glucose intolerance as evidenced by a random glucose of greater than 8.0 mmol/l. All patients were studied at a time when their chest symptoms were well controlled.

Eleven genetically unrelated controls (three males, eight females; mean age 14.3 years, range 10.8-24.4 years) were studied during the same period. These were friends of the patients or the children of members of staff. Attempts were made to select a group who were of a similar age and sex distribution as the cystic fibrosis patients.

Body weights were measured using a balanced scale (Seca model 220, Germany) and heights with a stadiometer (Seca model 220, Germany). The mid upper arm circumferences were measured with a tape measure to the nearest 0.1 cm and the mean circumference of both arms was used. The hand grip was assessed to the nearest 1.0 kg using a dynamometer (Stoelting Co). Triceps and subscapular skinfold thicknesses were measured by a single observer (IMB) using Harpenden skin calipers (John Bull; British Indicators Ltd) to the nearest 0.1 mm. Recent reports suggest that standard regression equations to derive body fat mass are invalid in cystic fibrosis patients¹⁵ and therefore skinfold thicknesses alone are presented. Muscle mass was calculated using the regression equations of Heymsfield *et al.*¹⁶ Patient details are given in tables 1, 3a, and 3b.

Consent for the study was obtained from both the patients and parents. The study was approved by the hospital ethics committee.

Methods

MEASUREMENT OF FUEL OXIDATION RATES

Respiratory gas exchange was measured by flow through indirect calorimetry using a commercially available system (Datex Deltatrac Metabolic

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Table 1 Growth and body composition of cystic fibrosis patients and control subjects

	Mean (SE) cystic fibrosis patients	Mean (SE) control subjects	Difference	95% CI for difference	Significance of difference (p value)
Age (years)	13.6 (0.8)	14.7 (1.1)	-1.1	(-3.9 to 1.7)	NS
Height (m)	1.50 (0.03)	1.57 (0.03)	-0.07	(-0.16 to 0.02)	NS
Weight (kg)	41.6 (2.6)	50.7 (3.3)	-9.1	(-17.8 to -0.32)	0.04
Body mass index (kg/m ²)	18.0 (0.6)	20.2 (0.7)	-2.1	(-4.1 to -0.2)	0.03
Surface area (m ²)	1.32 (0.01)	1.48 (0.01)	-0.16	(-0.33 to 0.003)	0.052
Handgrip (kg)	16.0 (1.7)	21.4 (2.7)	-5.4	(-12.2 to 1.4)	NS
Triceps skinfold (mm)	9.4 (1.1)	12.7 (1.5)	-3.3	(-7.8 to 0.6)	NS
Muscle mass (kg)	16.2 (0.9)	20.2 (1.3)	-4.0	(-7.3 to -0.6)	0.01
Muscle mass (% of body weight)	39.5 (1.0)	40.3 (1.5)	-0.7	(-4.4 to 2.9)	NS

CI=confidence intervals, NS=not significant.

Monitor, Datex Instrument Corporation). The studies were performed between 09.00 and 10.00 hours after a 12 hour overnight fast during which no routine medications were administered. Patients were in particular asked not to use β -agonist preparations as they have been reported to increase the basal metabolic rate.¹⁷

The patient lay quietly on a bed with an acrylic hood over the head and shoulders. The hood was ventilated with room air at 45 l/min using a constant air flow generator incorporated into the calorimeter. The precise flow rate was first determined by infusing known volumes of white spot nitrogen into the system.

Mixed expired air was analysed for oxygen using a differential paramagnetic analyser and carbon dioxide with an infrared sensor; both were incorporated into the metabolic monitor. These analysers were calibrated before use with a mixture of 95.0% oxygen and 5.0% carbon dioxide as recommended by the manufacturer. The precise composition of these calibration gases was predetermined using gravimetric methods to two decimal places by the supplier (Electrochem Ltd).

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide consumption ($\dot{V}CO_2$) were calculated at one minute intervals using a microprocessor and displayed both graphically and numerically on a visual display unit and digitally using a chart recorder. The first few measurements were discarded and readings were only used when a steady state was achieved. Measurements were then continued until at least six steady state recordings at one minute intervals had been made.

Urinary nitrogen excretion was measured over the same 12 hour period from a timed urine collection by the Kjeldahl method using an automated Kjeltac 1000 autoanalyser (Perstorp Analytical Ltd) with a coefficient of variation of <2%.

The rates of oxidation of fat, protein, and carbohydrate are calculated using standard formulas relating $\dot{V}O_2$, $\dot{V}CO_2$, and urinary nitrogen excretion to the oxidation of these fuels. These methods are comprehensively reviewed by Frayn,¹⁸ Elia and Livesey,¹⁹ and Ferrannini.²⁰ The constants used by Ferrannini were used in our calculations.

DIETARY INTAKE

Nutrient intake was estimated before the measurement of metabolic rate using a five day dietary diary. The intake of fat, protein, and carbohydrate was assessed over two periods; the entire five days of the dietary diary and the 24 hours before the metabolic study. The analysis was performed by a paediatric dietitian (SPW) using McCance and Widdowson nutrient data²¹ on the 'Microdiet' computer software.²²

DISEASE SEVERITY

Respiratory function tests were measured with a Vitalograph compact spirometer (Vitalograph). The results for forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were expressed as a percentage of reference values predicted for height, age, and sex based on the standards of Polgar and Promadhat.²³

Table 2 Clinical details and REE of cystic fibrosis patients

Patient No	Sex	FVC (% predicted)	FEV ₁ (% predicted)	Sputum culture	IgG (g/l)	Chrispin-Norman score	Shwachman score	Genetics	REE (% predicted)
1	M	105	83	PA	11.0	10	90	$\delta F508/\delta F508$	113.1*
2	M	98	92	PA	8.9	8	90	$\delta F508/?$	112.8*
3	M	84	73	ng	6.5	10	85	$\delta F508/\delta F508$	104.9
4	M	110	92	XM	9.2	4	95	I507/I717-1 (G>T)	116.6*
5	M	132	121	HI	9.8	3	95	$\delta F508/\delta F508$	109.0
6	M	114	95	ng	7.1	4	90	$\delta F508/\delta F508$	107.7
7	F	100	83	PA	10.0	7	85	$\delta F508/\delta F508$	92.8
8	F	86	59	PA	12.5	6	65	$\delta F508/\delta F508$	105.1
9	F	102	75	XM	11.9	6	85	$\delta F508/\delta F508$	100.0
10	F	56	37	PA	19.8	11	80	$\delta F508/?$	111.9*
11	F	109	88	ng	12.3	6	90	$\delta F508/\delta F508$	105.9
12	F	94	70	PA	8.7	3	95	$\delta F508/?$	121.8*
13	F	125	109	SA	9.0	8	85	$\delta F508/\delta F508$	105.1
14	F	106	98	HI	12.3	5	80	$\delta F508/?$	101.7
15	F	128	99	PA	15.2	15	80	$\delta F508/?$	96.7
16	F	140	110	PA	11.4	8	85	$\delta F508/\delta F508$	103.4

HI=Haeophilus influenzae, PA=Pseudomonas aeruginosa, SA=Staphylococcus aureus, XM=Xanthomonas maltophilia.

ng=No regular pathogen growth, ?=not known.

*Hypermetabolic.

Table 3 Anthropometry, respiratory gas exchange, and faecal fat for cystic fibrosis patients and anthropometry and respiratory gas exchange for control subjects

Patient/ subject No	Sex	Age (years)	Height (m)	Weight (kg)	MAC (ND) (cm)	TSF(ND) (mm) (centile)	SSF (mm) (centile)	Muscle mass (kg)	REE (% predicted)	REE (kJ/h/m ²)	RER	Faecal fat (g/day)
(a) Cystic fibrosis patients												
1	M	13.3	1.46	39.9	20.6	9.0 (75-90)	5.3 (10-25)	15.1	113.1	194.4	0.82	7.5
2	M	14.5	1.55	47.3	23.0	5.3 (10)	6.5 (25-50)	20.6	112.8	192.0	0.89	13.6
3	M	11.1	1.43	29.3	17.6	6.4 (10-25)	4.4 (10-25)	12.2	105.0	184.3	0.85	1.6
4	M	11.6	1.39	34.5	22.5	8.8 (50)	6.1 (50)	15.6	116.7	204.2	0.85	18.4
5	M	13.2	1.50	37.6	19.4	6.3 (10-25)	4.1 (<3)	14.9	109.0	186.7	0.82	21.6
6	M	12.4	1.38	32.7	20.5	5.5 (3-10)	4.6 (3-10)	15.1	107.7	187.7	0.88	
7	F	11.5	1.39	31.1	18.8	7.5 (10-25)	5.8 (10-25)	12.3	92.8	168.5	1.00	13.1
8	F	13.0	1.44	31.8	18.9	7.4 (3-10)	4.6 (<3)	12.7	105.1	185.3	0.82	6.7
9	F	15.0	1.62	51.4	24.7	21.4 (75-90)	9.5 (25-50)	16.1	100.0	155.9	0.83	15.9
10	F	15.9	1.67	58.4	26.0	12.9 (25-50)	7.5 (3-10)	23.4	111.9	170.7	0.80	23.6
11	F	12.3	1.59	50.2	23.6	8.1 (10-25)	7.9 (25-50)	20.3	105.9	168.5	0.82	13.2
12	F	10.5	1.60	57.2	25.3	11.5 (50)	10.4 (50-75)	21.2	121.8	193.1	0.86	27.8
13	F	11.6	1.42	31.6	19.3	7.8 (10-25)	5.9 (10-25)	12.9	105.2	188.4	0.80	6.3
14	F	12.8	1.43	31.4	19.0	6.7 (3-10)	4.5 (<3)	12.8	101.8	180.1	0.86	43.7
15	F	23.5	1.69	56.2	23.2	15.4 (25-50)	10.2 (25-50)	18.1	96.7	142.8	0.81	1.7
16	F	16.3	1.52	45.6	23.1	11.5 (10-25)	8.0 (3-10)	16.9	103.4	167.2	0.84	5.1
(b) Control subjects												
17	M	12.3	1.48	34.9	20.2	9.1 (50-75)	7.6 (50-75)	14.2	92.9	160.5	0.78	-
18	M	12.0	1.48	39.0	21.4	8.2 (25-50)	6.1 (25-50)	16.6	100.1	174.4	0.90	-
19	M	15.3	1.69	59.4	26.9	4.0 (<3)	6.1 (25)	29.5	101.4	171.3	0.78	-
20	F	14.3	1.48	48.7	28.2	21.8 (90-97)	21.1 (90-97)	19.1	88.0	144.9	0.76	-
21	F	14.4	1.68	59.6	25.2	16.0 (50-75)	21.7 (90-97)	20.3	101.8	155.2	0.79	-
22	F	14.8	1.67	60.8	26.0	17.5 (50-75)	16.2 (75-90)	20.9	96.1	146.3	0.78	-
23	F	12.2	1.55	47.7	24.9	11.8 (25-50)	13.6 (75-90)	21.0	90.0	145.8	0.85	-
24	F	24.4	1.66	63.1	28.5	15.2 (25-50)	13.2 (50-75)	25.2	96.6	142.7	0.84	-
25	F	10.8	1.38	34.1	22.2	9.0 (25)	8.5 (50-75)	15.5	90.9	163.7	0.80	-
26	F	14.4	1.62	60.8	26.4	12.6 (25-50)	13.7 (50-75)	22.4	102.8	159.5	0.84	-
27	F	16.9	1.64	49.7	22.5	11.6 (10-25)	7.7 (3-10)	18.2	92.4	142.5	0.81	-

MAC(ND)=mid upper arm circumference (non-dominant arm), TSF(ND)=triceps skinfold thickness (non-dominant arm), SSF=subscapular skinfold thickness, RER=respiratory exchange ratio.

Pulmonary function tests were not performed on the control subjects. However, none had asthma or was currently receiving medication for this or any other condition.

The Shwachman score, a clinical index of disease severity, was determined for each patient.²⁴ The chest x ray was scored by two observers using the method of Chrispin and Norman.²⁵

The most recent measurement of serum immunoglobulin IgG was obtained from the patients' case record. The patients' most recent routine daily faecal fat output measurement was used.^{26,27} These measurements had been made within six months of the study for 14 of the 15 cystic fibrosis patients for whom a result was available.

DNA ANALYSIS

Genomic DNA analysis was performed only for the subjects with cystic fibrosis. Although no control subject had a family history of cystic fibrosis, carriage of a cystic fibrosis allele could not be excluded in this group.

The patients' clinical details are shown in table 2.

STATISTICAL ANALYSIS

The data means for the two groups were compared using Student's *t* test for unpaired samples using the Minitab computer statistics package.²⁸

Results

The two groups were well matched for age and height (table 1), but the cystic fibrosis group had significantly lower body weight ($p<0.05$), and body mass index ($p<0.05$). Although muscle mass was significantly less in the cystic fibrosis group ($p<0.05$), when this was expressed as a percentage of body weight the two groups did not differ significantly. However, 10 of the cystic fibrosis patients had a triceps skinfold thickness less than the 25th centile compared with only two of the controls ($p<0.01$).²⁹ Ten cystic fibrosis patients also had a subscapular skinfold thickness below the 25th centile compared with only one of the control subjects ($p<0.01$). These data are shown in tables 3a and 3b.

The mean REE as predicted from the Harris-Benedict equation based on weight, height, age, and sex was significantly greater in the cystic fibrosis patients (106.8 *v* 95.7%; $p<0.001$).³⁰ The difference was also highly significant when

Table 4 REE and calculated fuel oxidation rates in cystic fibrosis patients and control subjects

	Mean (SE) cystic fibrosis patients	Mean (SE) control subjects	Difference	95% CI for difference	Significance of difference (<i>p</i> value)
REE (kJ/min)	3.93 (0.13)	3.84 (0.16)	0.09	(-0.34 to 0.53)	NS
REE (% Harris-Benedict)	106.8 (1.9)	95.7 (1.6)	11.1	(6.1 to 16.1)	0.0002
REE (kJ/h/kg)	5.85 (0.22)	4.65 (0.19)	1.20	(0.59 to 1.82)	0.0007
REE (kJ/h/m ²)	179.4 (4.0)	155.2 (3.5)	24.2	(12.3 to 35.1)	0.0002
REE (kJ/h/kg muscle mass)	14.8 (0.4)	11.6 (0.4)	3.2	(1.9 to 4.38)	0.00001
Non-protein respiratory quotient	0.85 (0.01)	0.81 (0.01)	0.03	(0.001 to 0.07)	0.06
Carbohydrate oxidation (%REE)	43.5 (4.2)	29.9 (4.4)	13.6	(1.0 to 26.0)	0.02
Protein oxidation (%REE)	15.4 (1.3)	18.9 (1.9)	-3.5	(-8.4 to 1.5)	NS
Fat oxidation (%REE)	41.1 (4.2)	51.1 (5.0)	-10.0	(-23.7 to 3.5)	NS

CI=confidence intervals, NS=not significant.

Table 5 Twenty four hour dietary intake for cystic fibrosis patients and control subjects

	Mean (SE) cystic fibrosis patients	Mean (SE) control subjects	Difference	95% CI for difference	Significance of difference (p value)
Protein (g/day)	75.8 (6.1)	74.2 (12.7)	1.6	(-28.6 to 31.8)	NS
Protein (g/kg/day)	1.94 (0.21)	1.55 (0.27)	0.39	(-0.33 to 1.11)	NS
Protein (% energy intake)	12.1 (0.6)	13.6 (1.1)	-1.5	(-4.2 to 1.1)	NS
Fat (g/day)	107.7 (7.6)	95.4 (12.0)	12.3	(-17.5 to 42.1)	NS
Fat (g/kg/day)	2.75 (0.27)	1.99 (0.31)	0.76	(-0.09 to 1.61)	NS
Fat (% energy intake)	38.4 (1.0)	40.2 (1.1)	-1.8	(-4.9 to 1.3)	NS
Carbohydrate (g/day)	337.0 (27.2)	255.5 (26.3)	81.5	(3.4 to 159.6)	0.049
Carbohydrate (g/kg/day)	8.54 (0.86)	5.32 (0.73)	3.22	(0.89 to 5.55)	0.009
Carbohydrate (% energy intake)	49.6 (1.2)	45.8 (1.4)	3.8	(0.003 to 7.6)	0.048
Energy intake (kJ/day)	10 686 (775)	8934 (1034)	1752	(-943 to 4447)	NS
Energy (kJ/kg/day)	272 (26)	186 (27)	86	(8 to 164)	0.03

CI=confidence intervals, NS=not significant.

REE was considered in relation to body weight ($p<0.001$), surface area ($p<0.001$), and muscle mass ($p<0.0001$) (table 4).

Measured values of REE are within $\pm 10\%$ of values predicted by the Harris-Benedict equation for all normal subjects. By this definition only five of the 16 patients with cystic fibrosis in our study were hypermetabolic (tables 2 and 3a). However, only one of these hypermetabolic patients (patient 10) had clinically important changes in respiratory function tests, chest x ray score, or IgG. All five were clinically infected with *Pseudomonas aeruginosa* or *Xanthomonas maltophilia* compared with only four of the 11 with an REE in the normal range. Only one of the five was homozygous for the $\delta F508$ mutation, compared with eight of the 11 who were not hypermetabolic ($p<0.05$).

The non-protein respiratory quotient was greater in the cystic fibrosis patients and the mean oxidation rate of carbohydrate expressed as a percentage of REE was also significantly greater (43.5 v 29.9% ; $p<0.05$) (tables 2, 3a, and 3b). The oxidation of fat was greater in the controls (41.1 v 51.1%), but this difference was not significant and the oxidation of protein was similar for the two groups.

The analyses of dietary intake are shown in tables 5 and 6. The patients with cystic fibrosis consumed more energy, fat, protein, and carbohydrate than the controls during both assessment periods. Carbohydrate intake as a proportion of total energy intake was significantly greater in the cystic fibrosis group during the 24 hours before the metabolic study (49.6 v 45.8% ; $p<0.05$).

Discussion

Our data are consistent with previous reports that mean REE is raised in cystic fibrosis patients compared with matched controls.³⁻⁵ The differences in REE were significant when expressed in terms of weight, body surface area, muscle mass, and predicted values derived from the Harris-Benedict equation. However, it should be noted that this equation predicts REE by taking account of weight, height, age, and gender but not body composition. The altered body composition of patients with chronic disease may result in a spurious increase in the estimation of REE. Nevertheless although the cystic fibrosis patients studied had reduced body fat compared with the controls, the patients who were hypermetabolic had generally normal skinfold thicknesses compared with the remainder of the cystic fibrosis group and indeed child 12, the patient with the highest REE, had triceps and subscapular skinfold thicknesses greater than the 50th centile.

The cystic fibrosis patients studied had lower body weights, skinfold thicknesses and muscle mass, although muscle mass as a percentage of body weight was similar. However, these are only indirect estimates of body composition and the use of more sophisticated measurements of body composition such as dual photon absorptiometry would be of interest to confirm these findings.

Several factors have been proposed to account for the raised REE in cystic fibrosis including an increased work of breathing due to chronic pulmonary disease, lung infection and inflammation, the effect of medication (particularly bronchodilators¹⁷), and a metabolic defect.^{4,6,8}

Table 6 Five day dietary intake for cystic fibrosis patients and control subjects

	Mean (SE) cystic fibrosis patients	Mean (SE) control subjects	Difference	95% CI for difference	Significance of difference (p value)
Protein (g/day)	84.9 (4.8)	69.9 (7.4)	15.0	(-3.6 to 33.6)	NS
Protein (g/kg/day)	2.16 (0.19)	1.48 (0.21)	0.68	(0.10 to 1.28)	0.02
Protein (% energy intake)	12.8 (0.4)	12.9 (0.6)	-0.1	(-1.7 to 1.5)	NS
Fat (g/day)	112.0 (8.1)	96.3 (7.8)	15.8	(-38.9 to 7.4)	NS
Fat (g/kg/day)	2.85 (0.30)	2.02 (0.26)	0.83	(0.01 to 1.64)	0.048
Fat (% energy intake)	37.7 (1.3)	40.7 (0.8)	-3.0	(-6.2 to 0.1)	NS
Carbohydrate (g/day)	352.8 (29.8)	258.8 (18.3)	94.0	(21.8 to 166.3)	0.02
Carbohydrate (g/kg/day)	8.94 (0.99)	5.34 (0.53)	3.6	(1.28 to 5.93)	0.004
Carbohydrate (% energy intake)	41.9 (1.5)	45.6 (1.1)	3.5	(-0.3 to 7.3)	NS
Energy intake (kJ/day)	11 281 (775)	8793 (664)	2488	(385 to 4592)	0.03
Energy (kJ/kg/day)	286 (28)	184 (21)	102	(29 to 176)	0.008

CI=confidence intervals, NS=not significant.

The variable correlation between REE and respiratory function tests suggests a wide range of REE at all levels of measured respiratory function. This is consistent with our observation that cystic fibrosis patients who are hypermetabolic may have normal pulmonary function on routine clinical tests. We believe that this may be related to the insensitivity of such tests to detect changes which may influence energy metabolism. Moreover the cystic fibrosis patients who were hypermetabolic all grew *P aeruginosa* or *X maltophilia* from their sputum and it seems likely that infection and lung inflammation was contributing to their increased REE, despite apparently mild chest disease. It remains appropriate therefore, for all cystic fibrosis patients, including those with mild chest disease, but especially those colonised by *Pseudomonas* species, to be encouraged to maintain a high energy intake.

Evidence for an energy consuming metabolic defect in cystic fibrosis is supported by a raised REE in patients homozygous for the commonest cystic fibrosis mutation, $\delta F508$, even after adjustment for pulmonary disease.⁸ The $\delta F508$ mutation involves a phenylalanine deletion within a nucleotide binding fold of the cystic fibrosis gene product, cystic fibrosis transmembrane conductance regulator (CFTR).³¹⁻³³ However, other mutations involve similar regions of the CFTR and this may be the explanation for the limited representation of patients homozygous for $\delta F508$ in our hypermetabolic group.

The effect of the preceding day's diet and energy intake on REE has not previously been considered in cystic fibrosis. One report suggests that REE may be influenced for at least 14 hours after the last meal³⁴ and this may have been relevant in patients consuming a high energy diet. However, others have not confirmed such an effect.³⁵⁻³⁸ We observed no relationship between REE as percentage predicted and energy consumed in the 24 hours before metabolic study ($r=0.16$).

Carbohydrate formed a greater proportion of the energy substrate in the cystic fibrosis patients after an overnight fast, which is in keeping with the findings of others.^{5,7,8} It seems likely that diet contributed to this as the patients with cystic fibrosis consumed a significantly greater proportion of their energy intake as carbohydrate during the 24 hours before the metabolic study. However, taken over the whole five day dietary assessment the proportion of energy derived from carbohydrate was not significantly different from the controls. Other workers have found no difference in the food quotient between cystic fibrosis patients and controls over a seven day period.⁸

Other factors may have had an important bearing on these dietary differences. Altogether 85-90% of those with cystic fibrosis and all the cystic fibrosis patients studied here have pancreatic insufficiency.³⁹ However, the malabsorption of fat, protein, and carbohydrate is variable and thus the actual proportion of energy available from dietary carbohydrate is likely to be greater than the dietary differences would suggest. Moreover, it has also been suggested that

carbohydrate transport across the intestinal mucosa is increased in individuals with cystic fibrosis^{40,41} which would exaggerate further the differential absorption of dietary carbohydrate compared with fat. The high carbohydrate availability could result in increased glycogen stores^{42,43} and reduce the tendency to oxidise fat after an overnight fast. It has been proposed that there may also be an additional increase in glycogenolysis in those with cystic fibrosis as a result of increased adrenaline secretion.⁷

Two important complications of cystic fibrosis may not have been detected by the criteria for inclusion in this study. Glucose intolerance is reported in 26% of cystic fibrosis patients,⁴⁴ but this is unlikely to be responsible for the increased carbohydrate oxidation observed as such patients are likely to have lower plasma concentrations of insulin and consequently increased fat oxidation after an overnight fast.

Early liver disease in the cystic fibrosis patients is often focal and may not have been apparent on clinical examination or biochemical liver function tests.⁴⁵ However, indirect calorimetry studies on adults with liver disease and cirrhosis have shown an increased oxidation of fat, probably because of reduced glycogen stores⁴⁶ and, therefore, it would seem unlikely that undetected liver disease would have accounted for the increased carbohydrate oxidation in the cystic fibrosis group.

Sources of error in measurements of metabolic rate by indirect calorimetry should be considered. Both hyperventilation and lactic acid accumulation increase the elimination of carbon dioxide resulting in a falsely high respiratory quotient. However, our readings were taken during a steady state with no subject having shown breathing difficulties and as the subjects were not exercised lactic acid accumulation was unlikely.

SUMMARY

The increase in REE observed by others has been confirmed for a group of mildly affected cystic fibrosis patients. Routine clinical methods of monitoring chest disease were unable to distinguish most of the cystic fibrosis patients with a raised REE, but these methods may be too insensitive to detect changes in the disease state that affect energy metabolism. However pulmonary infection and inflammation may be an important factor in the raised REE of these cystic fibrosis patients.

Carbohydrate oxidation represented a greater proportion of the REE in the cystic fibrosis group and this seems unlikely to be due to carbohydrate intolerance or liver disease. However, a diet relatively high in carbohydrate content, and better intestinal absorption of carbohydrate, may contribute to its increased use.

The importance of a high energy intake in cystic fibrosis is emphasised by these studies; however more attention to the utilisation of the various dietary fuels is still needed.

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