ELSEVIER
Journal of Cystic Fibrosis 5 (2006) 105 – 112
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

# The systemic inflammatory response to exercise in adults with cystic fibrosis ☆

Alina A. Ionescu [a,*], Timothy D. Mickleborough [b], Charlotte E. Bolton [a], Martin R. Lindley [b], Lisette S. Nixon [a], Gareth Dunseath [c], Steve Luzio [c], David R. Owens [c], Dennis J. Shale [a]

[a] *Respiratory Medicine, Cardiff University, Academic Centre, Llandough Hospital, Cardiff, CF64 2XX, United Kingdom*
[b] *Department of Kinesiology, Indiana University, Bloomington, IN 47401, United States*
[c] *Diabetes Research Unit, Cardiff University, Academic Centre, Llandough Hospital, Cardiff, CF64 2XX, United Kingdom*

Received 3 August 2005; received in revised form 27 November 2005; accepted 28 November 2005
Available online 3 January 2006

**Abstract**

Exercise is associated with release of inflammatory mediators in the circulation and there is evidence that the exercising muscles and tendons are sources of interleukin-6. Due to the catabolic effects of some cytokines, increased release in circulation might contribute to alterations in body composition in adults with cystic fibrosis. We hypothesised that exercise of moderate intensity would generate increased blood concentrations of some inflammatory mediators.

We investigated the change in blood concentrations of interleukin-6, tumour necrosis factor alpha and their soluble receptors after a structured exercise (box stepping) of intensity similar to that encountered during activities of daily living in 12 adults with cystic fibrosis and mean (95% confidence interval) $FEV_1$ 55.6 (44.4, 66.8)% predicted, body mass index 23.0 (21.3, 24.6) $kg/m^2$ and 12 healthy subjects.

The increments post-exercise for all inflammatory mediators and lactate corrected for the work performed until voluntary exhaustion were greater for patients, while the total work was less for patients (all $p < 0.01$). Daytime variability of the inflammatory mediators was assessed in eight patients and was less than the change due to exercise.

We report greater increments in circulating concentrations of some cytokines with moderate exercise in adults with cystic fibrosis compared to healthy subjects.


*Keywords:* Interleukin-6; Lactate; Box stepping; Work

## 1. Introduction

Strenuous exercise in healthy individuals is associated with an increase in the circulating concentrations of interleukin (IL)-1β, IL-6, tumour necrosis factor-α (TNFα), TNFα soluble receptor I (srI) and IL-1β receptor antagonist [1]. The increase in IL-6 is the most consistently reported response and is greater than changes reported for the other cytokines [2]. There is considerable evidence that IL-6 is released from exercising muscle and tendons [3,4]. The mechanism underlying this effect of exercise is unknown, though muscle injury and repair, increased circulating catecholamines and a homeostatic response to maintain glucose supply to exercising muscle have been suggested [5]. Whatever the mechanism, it is well established that the increase in IL-6 is related to muscle contractions, to the type of exercise and to the intensity and duration of exercise [6,7].

There are few reports of the cytokine response to exercise in disease states. Cooper and colleagues studied children with CF expecting a blunting of the IL-6 response to exercise secondary to raised circulating concentrations, compared with healthy subjects [8,9]. Most adults with CF and chronic pulmonary infection have increased levels

☆ Supported by Glaxo Smith Kline, Astra-Zeneca (UK), the British Lung Foundation and the British Thoracic Society. Results of this study have been shown in part in abstract form at the ATS Conference, Orlando 2004.
* Corresponding author. Tel.: +44 29 20716948; fax: +44 29 20716416.
*E-mail address:* ionescuaa@cardiff.ac.uk (A.A. Ionescu).

1569-1993/$ - see front matter © 2005 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.jcf.2005.11.006

of circulating inflammatory mediators when clinically stable, which increase further during exacerbations of their respiratory symptoms [10,11]. Cross-sectional studies reported that increased levels of circulating inflammatory mediators were related to markers of bone and cellular protein catabolism and associated with loss of fat free mass and reduced bone mineral density [10,12,13]. Additionally a longitudinal study in CF found that persistently high concentrations of immunoreactive IL-6 were related to a low bone mineral content and urinary excretion of a bone resorption marker [14]. Similar relationships between increased circulating IL-6 and TNFα and a reduced skeletal muscle mass and strength have been reported in healthy elderly subjects and patients with COPD [15,16]. TNFα and IL-6 were associated to increased protein catabolism and cachexia [8,17,18]. Such studies offer circumstantial evidence that some inflammatory mediators may play a part in the systemic complications of chronic respiratory disease.

We hypothesised that adults with CF with a background chronic acute phase like inflammatory response, parallel catabolic intermediary metabolism and a likely lower threshold for lactate production with exercise would have greater increments in IL-6, TNFα and their soluble receptors, compared with healthy age matched subjects, for the total work performed during an episode of moderate exercise. Additionally, we expected a relationship with lactate production and the cardio-respiratory response to exercise. To test this we assessed the inflammatory response to a structured exercise test of an intensity similar to that encountered during activities of daily living.

## 2. Methods

### 2.1. Subjects

Twelve patients (6 male) with CF were studied after 14 days inpatient intra-venous antibiotic treatment for an exacerbation of respiratory symptoms, when they were likely to be at their best clinical status [10,11]. All patients had a minimum of three isolations of *Pseudomonas aeruginosa* from sputum in the preceding 6 months. Patients had been diagnosed with CF according to the following criteria: clinical findings, sweat $Na^+$ and $Cl^- > 70$ mmol/l and all had a genotype ΔF508/ΔF508. Exclusion criteria were long-term oral corticosteroid or non-steroidal anti-inflammatory medication, diabetes mellitus, liver cirrhosis, chronic respiratory failure or cor pulmonale.

An exacerbation was defined as increased cough and sputum production, loss of appetite with or without weight loss and a reduction in $FEV_1$ of more than 10% from the usual value.

Twelve healthy subjects (5 male) not on a regular exercise programme were also studied. The study had Local Research Ethics Committee approval and participants gave written informed consent.

### 2.2. Protocol

Subjects were studied after a 15 min seated rest and at least 2 h post-prandial. Blood was obtained pre-exercise, post exercise, 30 and 120 min later from a cannulated hand vein. Subjects box-stepped (height 20 cm) at 15 steps/min set by a metronome and were encouraged to keep their trunk erect and unsupported. A maximum time of 20 min was set for the exercise, otherwise subjects could stop if exhausted, and the reason for stopping the test was documented. Oxygen uptake ($VO_2$) and carbon dioxide output ($VCO_2$) were measured wearing a mask during the last 2 min of rest, during exercise and through the recovery period until $VO_2$ was within 10% of the pre-exercise values (K4b, Cosmed, Italy). Measurements were made continuously during exercise, but only those of the last minute were analysed. Oxygen saturation was measured by finger pulse oximetery (Critikon, Ohio). At the end of the exercise breathlessness was assessed using the 10 point Borg scale.

Since the type of exercise (i.e. high work rate in short bouts, or endurance-type) likely to trigger cytokine release in patients with lung disease is largely unknown, we chose to exercise subjects at a constant work rate (power) and the total work performed was calculated.

Total work performed (kJ) = Power (W) * time (s), where the power (W) = height of the step (m) * number of steps/minute * subject's weight (kg) * 0.163 [19]. The work rate (in metabolic equivalents-Mets, 1 Met = 3.6 ml/kg/min) for the last minute of exercise was calculated [20]. We used this conversion as an estimate to allow us to compare the work rate during exercise with work rates of habitual physical activities recorded by questionnaire.

### 2.3. Repeatability of cytokine measures

Eight patients had repeated measurements of circulating concentrations of inflammatory mediators. The inflammatory mediators were measured on three occasions, 2 weeks apart, in the morning and fasting conditions. All measurements were recorded during clinical stability.

### 2.4. Other measurements

Habitual physical activity was assessed by questionnaire and expressed in Mets [21]. Height, weight and body mass index (BMI, $kg/m^2$) were measured, fat free mass index (FFMI) was derived from two site-skinfold thickness and $FEV_1$ was measured by spirometry.

### 2.5. Circulating biochemical parameters and inflammatory mediators

Blood lactate was determined colorimetrically using lactate oxidase (Pointe Scientific, USA). Glucose was determined enzymatically using hexokinase (Diasys Diagnostic Systems GmbH (Germany). Insulin-like growth

factor 1(IGF-1) was measured by an immunoenzymometric assay (IEMA), Immunodiagnostic Systems Ltd (IDS) (UK) and cortisol by a solid phase Radioimmunoassay (RIA), Diagnostic products corporation (DPC) (USA).

Interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFα) were measured by high sensitivity ELISA kit (R&D systems Europe), assayed once in duplicate. TNFα soluble receptors (sr) I and II were measured by ELISA CytoSets (BioSource Europe, Nivelles, Belgium).

IL-6 sr was determined by in house ELISA. Results were the mean of two results when samples were assayed in duplicate.

The intra and inter assay coefficient of variation (CV) were both <10% for all assays.

### 2.6. Statistical analysis

The incremental change in lactate, inflammatory mediators, hormones and the decrement in $SaO_2$ due to exercised were expressed as a ratio of the total work done, to allow comparisons to be made despite differences in the total work performed. Increment=(post exercise value−pre-exercise value)/total work done.

Analysis was performed with the SPSS software, version 10. Data is presented as arithmetic means and 95% confidence intervals (95% CI). Analysis of variance and the post hoc Tukey's test were used to compare patients with healthy subjects. ANOVA with Friedman's test followed by Wilcoxon test for two related samples was performed for repeated measurements. Multiple stepwise regression was used to investigate relationships between variables.

## 3. Results

Only 11 patients were included in the final analysis because of non-specific cross-reactivity in the IL-6 assay, which led to unreliable results for one patient. The BMI and FFMI were similar for patients and healthy subjects (Table 1). Patients had lower levels of habitual physical activity than the healthy subjects ($p<0.01$, Table 1). The total work performed and the duration of exercise was greater for healthy subjects (all but 2 completed 20 min of exercise), but the work rate was not different between patients and healthy subjects (Table 1). None of the patients completed 20 min of exercise. One patient completed 19 min, the mean exercise time for patients was 4.80 min (Table 1). The level of habitual physical activity ($r^2=0.78$, $p<0.001$) and FFMI ($r^2=0.34$, $p<0.01$), but not $FEV_1$ ($r^2=0.21$, $p=0.08$) were determinants for the work done by the patients.

### 3.1. Respiratory response to exercise

Oxygen uptake during the last minute of exercise and the $VO_2$ increment after exercise was greater for healthy subjects than patients (Table 1). The rise in oxygen uptake, VT, respiratory rate and heart rate per kilo-Joule (kJ) of work done, were greater for patients (Table 1). Oxygen saturation ($SaO_2$) was less at the end of exercise compared to baseline for patients than for healthy subjects (94.6 (93.0, 96.3)% compared with 97.8 (97.0, 98.7)%, $p<0.05$), and at the end of exercise 90.9 (87.3, 94.6) and 95.0 (94.1, 95.4) for patients and healthy subjects, respectively. The exercise decrement in $SaO_2$/kJ of work done was greater for patients than healthy subjects; 2.16 (0.23, 4.08) and 0.20 (0.12, 0.28)%/kJ, $p<0.05$. For the patients, $FEV_1$ ($r^2=0.70$, $p<0.001$) was a determinant of the reduction in $SaO_2$ with exercise. The Borg score at the end of exercise was greater for patients ($p<0.01$), Table 1.

The work performed, expressed in metabolic equivalents (Mets), was greater for healthy subjects (Table 1).

Table 1
Anthropometrics, dyspnoea and physical activity scores, ventilatory parameters in patients and healthy subjects; *$p<0.01$ between patients and healthy subjects (ANOVA followed by Tukey's test)

| Mean (95% CI) | Patients ($n=11$) | Healthy subjects ($n=12$) |
|---|---|---|
| Age (years) | 28.2 (23.3, 32.9) | 29.9 (26.0, 33.7) |
| $FEV_1$ (% predicted) | 55.6 (44.4, 66.8) | |
| BMI (kg/m$^2$) | 23.0 (21.3, 24.6) | 25.2 (22.5, 27.8) |
| FFMI (kg/m$^2$) | 15.6 (14.6, 16.5) | 16.5 (15.7, 17.2) |
| Total work performed (kJ) | 9.52 (1.49, 17.56)* | 40.3 (33.5, 47.2) |
| Exercise duration (s) | 288.5 (72.8, 504.24)* | 1145.0 (1071.4, 1218.5) |
| Work rate (power, W) | 31.2 (27.6, 34.6) | 35.1 (29.9, 40.3) |
| Borg score (10 point scale) | 6.3 (5.6, 7.2)* | 4.6 (3.4, 5.9) |
| Habitual activity (Mets) | 38.2 (30.3, 46.2)* | 64.7 (57.6, 71.8) |
| Lactate end of exercise (mmol/l) | 3.6 (2.5, 4.6) | 2.8 (1.9, 3.6) |
| $VO_2$ end of exercise (ml/kg/min) | 14.3 (10.8, 17.8)* | 21.5 (19.7, 23.3) |
| $VO_2$ uptake (increment, l/kJ) | 1.69 (1.11, 2.27)* | 0.48 (0.39, 0.56) |
| Respiratory rate increment, rate/min/kJ | 2.33 (1.12, 3.54)* | 0.32 (0.24, 0.41) |
| VT increment, l/kJ | 0.046 (0.033, 0.058)* | 0.021 (0.018, 0.024) |
| METs of work performed | 3.098 (3.01, 4.95)* | 5.97 (5.48, 6.47) |
| Heart rate increment, rate/min/kJ | 7.5 (4.3, 10.8)* | 1.7 (1.4, 2.1) |

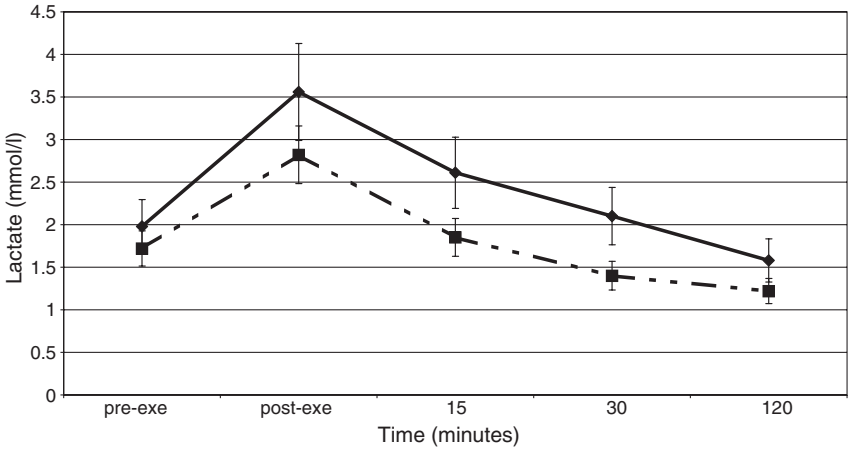


Fig. 1. Lactate concentrations at baseline, after exercise and 15, 30 and 120 min later. Continuous line—patients, interrupted line—healthy subjects. Data presented as means and confidence intervals. Comparison between patients and healthy subjects was performed by ANOVA and post-hoc Tukey's test.

### 3.2. Lactate response to exercise

Plasma lactate levels were not different between patients and healthy subjects at any assessment (Fig. 1). The lactate increment at the end of exercise for patients and healthy subjects was 1.58 (0.58, 2.58) and 1.10 (0.27, 1.93) mmol/l, respectively. However, when related to the work done, the increment was greater in patients than healthy subjects, 0.23 (0.08, 0.37) and 0.03 (0.006, 0.027) mmol/l/kJ, respectively, $p<0.01$. The work done ($r^2=0.71$, $p<0.01$) and habitual physical activity (Mets) ($r^2=0.72$, $p<0.01$) were determinants of the lactate increment with exercise in the patients only, but not the $FEV_1$ ($r^2=0.11$) or $SaO_2$ ($r^2=0.02$).

### 3.3. Inflammatory mediator and hormone responses to exercise

The pre- and post-exercise concentrations of IL-6 ($p<0.01$), TNFα and soluble receptors (sr I and II) ($p<0.05$) were greater for patients than healthy subjects (Table 2). Peak values for inflammatory mediators occurred at the completion of exercise in both patients and healthy subjects (Table 2). For the patients IL-6 ($p<0.01$), IL-6 sr ($p<0.05$) and TNFα sr I ($p<0.05$) were greater at the end of exercise compared with pre-exercise, while in the healthy subjects only IL-6 and IL-6 sr (both $p<0.01$, Fig. 2) were greater at the end of exercise. The end of exercise increment corrected for the work done was greater for patients for IL-6, IL-6 sr, TNFα, TNFα srI and II (all $p<0.01$, Fig. 3).

In the 2 h post exercise period IL-6 levels remained greater than at pre-exercise at 30 ($p<0.01$) and 120 min ($p=0.016$) for patients, but only at 30 min ($p<0.05$) for the healthy subjects (Fig. 2). At 120 min IL-6 levels had not returned to baseline in the patients. The absolute concentrations of all other inflammatory mediators were not different from baseline at 30 and 120 min. The absolute lactate increment had an effect on the absolute IL-6 increment ($r^2=0.44$, $p<0.01$) for patients and healthy subjects as a group ($n=23$), while the total work done had an effect on the IL-6 increment only for patients ($r^2=0.74$, $p<0.01$).

Table 2
Inflammatory mediators and hormone concentrations in patients and healthy subjects at start and end of exercise; *$p<0.05$; **$p<0.01$ (comparing patients with healthy subjects by ANOVA followed by Tukey's test)

| Mean (95% CI) | Patients | Healthy subjects |
|---|---|---|
| IL-6 (pg/ml) start** | 3.73 (2.04, 5.43) | 1.01 (0.60, 1.42) |
| End** | 5.23 (3.35, 7.10) | 1.24 (0.84, 1.64) |
| TNFα (pg/ml) start* | 3.30 (1.90, 4.78) | 1.78 (1.32, 2.25) |
| End* | 3.34 (1.99, 4.69) | 1.79 (1.24, 2.34) |
| IL-6 sr (pg/ml) start | 42.8 (38.4, 47.3) | 36.7 (28.6, 44.8) |
| End | 47.6 (41.3, 53.9) | 41.7 (34.7, 48.6) |
| TNFα srI (ng/ml) start* | 1971.6 (1350.3, 2593.0) | 1543.6 (1025.0, 2062.3) |
| End* | 2319.2 (1615.9, 3022.5) | 1898.2 (852.8, 2943.5) |
| TNFα srII (ng/ml) start* | 5111.0 (4012.4, 4620.9) | 3019.1 (2194.1, 3844.2) |
| End* | 5028.5 (3907, 6149.4) | 3158.7 (2072.1, 4245.3) |
| IGF1 start | 128.6 (95.4, 161.8) | 125.4 (97.1, 153.7) |
| End | 114.8 (91.0, 138.6) | 117.1 (93.4, 140.8) |
| Cortisol start | 9.7 (6.1, 13.3) | 12.0 (9.6, 14.4) |
| End | 10.5 (7.5, 13.4) | 11.0 (8.7, 13.3) |

All peak concentrations occurred at the end of exercise.

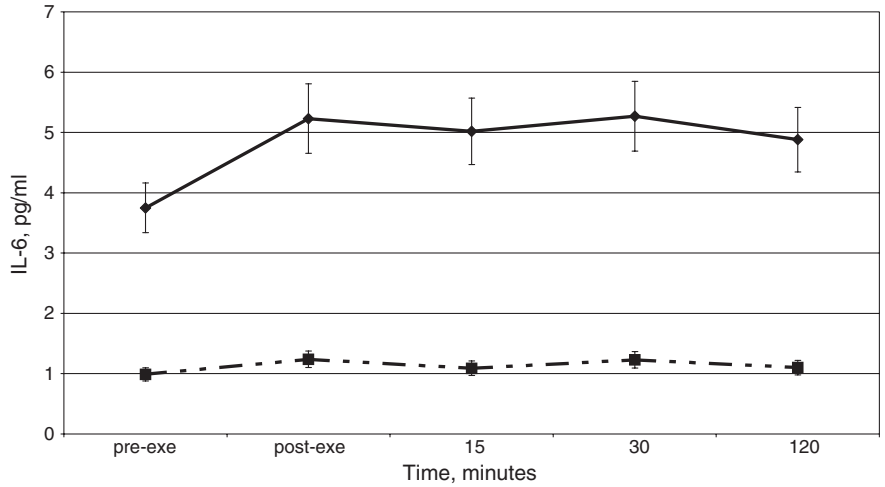


Fig. 2. IL-6 concentrations at baseline, after exercise and 15, 30 and 120 min later. Continuous line—patients, interrupted line—healthy subjects. Data presented as means and confidence intervals. IL-6 was greater at the end of exercise than at baseline for both patients and healthy subjects ($p < 0.01$).

Pre-exercise IGF1 and cortisol concentrations were similar in patients and healthy subjects and remained so at all determinations (Table 2). There was no difference between the pre-exercise levels of IGF1 or cortisol and the levels 2 h later. Blood glucose was unchanged at the end of exercise compared to pre-exercise, for patients or healthy subjects.

### 3.4. Variability of the inflammatory mediators

For the eight patients who had repeated measurements in a resting state, no difference was found at any assessment point for any inflammatory mediator during the three days (Friedman tests $p$ non-significant). The greatest variability was in IL-6 concentrations; mean (95% CI) ratio between two consecutive measurements, where the greatest variation was found, was 1.2 (1.1, 1.3), less than the response found with exercise in patients, where the mean ratio between IL-6 concentration at the end and at the start of exercise was 1.47 (1.2, 1.91), while for healthy subjects it was 1.2 (1.12, 1.39). For all other inflammatory mediators the variability between assessments was less than for IL-6 (Table 3).

## 4. Discussion

Low intensity exercise to subject defined exhaustion was associated with a greater plasma lactate, pro-inflammatory/pro-catabolic cytokine and anabolic and catabolic hormone response in adults with CF compared with healthy subjects completing greater amounts of exercise. The disproportionate rise in lactate, IL-6, TNFα and their soluble receptors for the work done confirms the reported response to exercise in children with CF with mild to moderate severity lung disease [8] and is similar to reported changes in adults with COPD [22–24]. Female athletes with CF have disturbed energy metabolism at a cellular level, despite normal lung

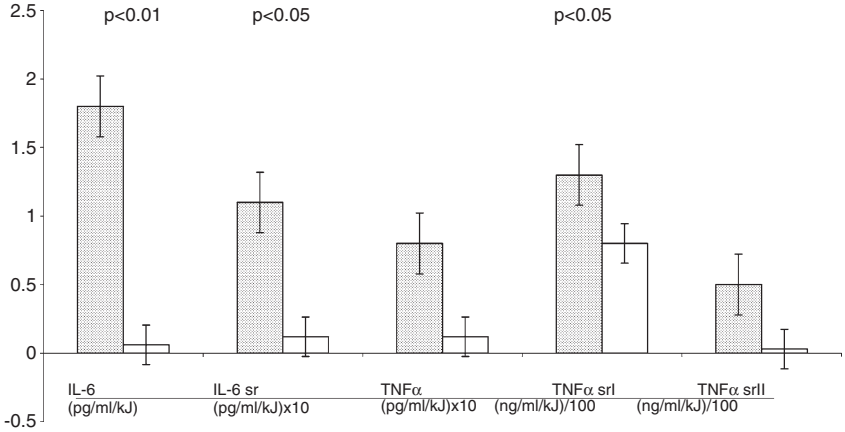


Fig. 3. Post-exercise increment in inflammatory mediators. The increment was calculated for each inflammatory mediator as follows: (concentration at the end of exercise − concentration before exercise)/work performed and expressed in units/kilo-Joule work. Results are presented as means and standard error bars, grey columns—patients; white columns—healthy subjects. ANOVA with Friedman's test followed by Wilcoxon test for two related samples was performed for comparisons between pre and post-exercise.

Table 3
Daytime variability of inflammatory mediators (the table illustrates variability during day 1, similar variability observed during days 2 and 3, each assessment 2 weeks apart and while resting)

| Mean (95% CI) | Baseline | 15 min | 30 min | 45 min | 60 min | 90 min | 120 min |
|---|---|---|---|---|---|---|---|
| IL-6 (pg/ml) | 11.1 (2.9, 19.4) | 11.5 (2.4, 20.7) | 11.4 (2.7, 20.1) | 11.5 (3.6, 19.3) | 11.9 (3.2, 20.5) | 12.3 (2.8, 21.8) | 12.7 (3.6, 21.9) |
| IL-6 sr (pg/ml) | 23.1 (20.2, 26.1) | 24.0 (19.0, 29.0) | 23.9 (18.7, 29.0) | 24.7 (19.8, 29.5 | 23.8 (18.9, 28.6) | 25.0 (19.7, 30.3) | 23.6 (19.1, 28.1) |
| TNFα (pg/ml) | 2.42 (1.17, 3.67) | 2.41 (1.27, 3.54) | 2.31 (1.07, 3.55) | 2.30 (1.15, 3.48) | 2.38 (1.19, 3.57) | 2.32 (1.09, 3.55) | 2.33 (1.07, 3.58) |
| TNFα srI (ng/ml) | 1344.2 (940.5, 1747.9) | 1192.0 (878.9, 1505.0) | 1265.8 (756.8, 1774.8) | 1187.1 (761.9, 1612.3) | 1144.8 (720.6, 1569.1) | 1118.5 (812.6, 1424.4) | 1294.1 (908.8, 1679.3) |
| TNFα srII (ng/ml) | 4797.8 (3340.2, 6255.5) | 4288.8 (2791.7, 5785.9) | 4698.8 (3296.6, 6101.0) | 4147.2 (2798.1, 5496.4) | 4417.0 (3284.8, 5549.1) | 4379.7 (3220.8, 5538.6) | 4101.6 (2861.0, 5342.1) |

function, suggestive of a malfunction of the mitochondrial metabolism possibly linked to the lactate increment with exercise [9].

Since the type of exercise likely to trigger an immediate cytokine release in patients with lung disease is uncertain, we chose to exercise subjects at a constant individual work rate from which the total work performed was calculated rather than use maximum exercise to exhaustion [8]. This design allowed patients to exercise for a sufficient period to obtain data, despite their ventilatory limitation, and achieve a total work performance similar to that of light activities of daily living, such as driving, lifting light objects and vacuuming or ironing [20,21]. The conversion of work rate into Mets and comparison with the habitual activity Mets score indicated this criterion was achieved in this study. However, comparison of the energy costs of the exercise performed with the energy costs of daily activities needs to be interpreted cautiously. The METs for daily activities were calculated for non-CF individuals, while no data is available for CF patients who have an increased resting energy expenditure (REE). We used the METs simply to assess the amount of exercise performed in metabolic equivalents, which is unlikely to be dependent on the REE. The lack of difference in absolute lactate levels between patients and healthy subjects indicates that similar levels of metabolic stress occurred in each individual in response to exercise. However, the patients only completed approximately 25% of the work done by the healthy subjects. It is likely that the greater lactate response per unit of work in our patients was due to impaired ventilation, reduced aerobic reserve, metabolic changes in the exercising muscles involved and altered oxygen uptake [8,9]. The oxygen uptake (ml/kg/min) at the end of the exercise was significantly lower in the patients compared to the healthy subject. However, when reported as a ratio to the work performed the oxygen uptake was greater for the patients, suggesting that for the same work rate patients utilised more aerobic energy [8].

The greater IL-6, TNFα, TNFα sr I and II increment for work performed in the patients suggests a lower threshold for cytokine response in patients. We assessed the increment rather than the absolute increase in the inflammatory mediators in order to be able to compare the magnitude of response to exercise, irrespective of the pre-exercise level, to allow comparisons between patients and healthy individuals who have different circulating levels of inflammatory mediators. The persistence of the IL-6 response over the 2 h post-exercise observation period was similar to the IL-6 response to running in healthy subjects, but for lesser total work [7]. In healthy subjects the increase in circulating IL-6 may be immediate or delayed up to 2 h after completing the exercise depending on the type undertaken [25]. Immediate release of IL-6 may stimulate hepatic glycogenolysis to maintain blood glucose and the uptake of glucose by exercising muscles while later release of IL-6 may be related to muscle injury and be important in muscle training. In both patterns the effect of the increase in IL-6 is considered

to be advantageous by its action on the hypothalamic–pituitary–adrenal axis with increased secretion of ACTH and consequently glucocorticoids, which may provide either improved substrate availability or an anti-inflammatory response to increased pro-inflammatory, pro-catabolic cytokines in skeletal muscle [26].

In contrast, increased levels of circulating IL-6 and TNFα were associated with a reduced body cell and skeletal muscle mass, reduced muscle strength and increased mortality in healthy elderly subjects suggesting a possible link to age related sarcopenia [15,27,28]. In patients with CF and COPD increased circulating levels of IL-6, TNFα and their soluble receptors were associated with a reduced FFM, skeletal muscle and bone mass, and an increased number of exacerbations [12,14,16]. In particular, these associations with a low FFM held in patients when clinically stable [12]. Increased circulating TNFα in patients with HIV was related to impaired protein synthesis in skeletal muscle after treatment with growth hormone and TNFα sr were raised in all clinical stages, but greatest in AIDS where they indicate disease progression [29]. Further support for a potentially disadvantageous effect of systemic inflammation comes from the IL-6 transgenic mouse which constitutively secretes IL-6 and develops a severe proteolytic myopathy, reversed by an IL-6 receptor blocking antibody, which indicates a role for IL-6 in muscle mass regulation [30]. In vitro and in vivo studies with myocytes suggest that both IL-6 and TNFα may have regulatory roles at a molecular level in the maintenance of skeletal muscle status [31–35]. Hence, our observation that increased IL-6, TNFα and their soluble receptors following exercise occurs at a lower threshold in patients may be of pathophysiological relevance.

Our findings demonstrate a resetting of the threshold for the cytokine and lactate response to exercise in adults with CF and moderate lung function impairment. In advancing disease the lower threshold for the cytokine and the persistence of such circulating mediators may allow such cytokine surges to have catabolic effects and add to other mechanisms underlying muscle loss, reduction in bone mineral density, cachexia and physical disability in chronic respiratory diseases. Further studies of these relationships may indicate avenues for therapeutic interventions to maintain muscle mass and function [36–38].

## Acknowledgements

We would like to thank Dr. Timothy L. Griffiths for advising on the study protocol.

## References

[1] Ronsen O, Lea T, Bahr R, Pedersen BK. Enhanced plasma IL-6 and IL-1ra responses to repeated vs. single bouts of prolonged cycling in elite athletes. J Appl Physiol 2002;92:2547–53.

[2] Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, Pedersen BK. Production of interleukin-6 in contracting human skeletal muscle can account for the exercise-induced increase in plasma inteleukin-6. J Physiol 2000;529:237–42.

[3] Keller P, Keller C, Carey AL, Jauffred S, Fischer CP, Steensberg A, et al. Interleukin-6 production by contracting skeletal muscle autocrine regulation by IL-6. Biochem Biophys Res Commun 2003;310:550–4.

[4] Penkowa M, Keller C, Keller P, Jauffred S, Pedersen BK. Immunohistochemical detection of interleukin-6 in human skeletal muscle fibres following exercise. FASEB J 2003;17:2166–8.

[5] Lancaster GI, Jentjens RLPG, Moseley L, Jeukendrup AE, Gleeson M. Effect of pre-exercise carbohydrate ingestion on plasma cytokine, stress hormone and neutrophil degranulation responses to continuous, high-intensity exercise. Int J Sport Nutr Exerc Metab 2003;13:436–53.

[6] Willoughby DS, McFarlin B, Bois C. Interleukin-6 expression after repeated bouts of eccentric exercise. Int J Sports Med 2003;24:15–21.

[7] Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. J Physiol 1998;508:949–53.

[8] Tirakitsoontorn P, Nussbaum E, Moser C, Hill M, Cooper DM. Fitness, acute exercise and anabolic and catabolic mediators in cystic fibrosis. Am J Respir Crit Care Med 2001;164:1432–7.

[9] Selvadurai HC, Allen J, Sachinwalla T, Macauley J, Blimkie CJ, Van Asperen PP. Muscle function and resting energy expenditure in female athletes with cystic fibrosis. Am J Respir Crit Care Med 2003;168:1476–80.

[10] Ionescu AA, Nixon LS, Evans WD, Stone MD, Lewis-Jenkins V, Chatham K, et al. Bone density, body composition and inflammatory status in cystic fibrosis. Am J Respir Crit Care Med 2000;162:789–94.

[11] Bell SC, Bowerman AM, Nixon LS, Macdonald IA, Elborn JS, Shale DJ. Metabolic and inflammatory responses to pulmonary exacerbation in adults with cystic fibrosis. Eur J Clin Invest 2000;30:553–9.

[12] Ionescu AA, Nixon LS, Luzio S, Lewis-Jenkins V, Evans WD, Stone MD, et al. Pulmonary function, body composition and protein catabolism in adults with cystic fibrosis. Am J Respir Crit Care Med 2002;165:495–500.

[13] Aris RM, Renner JB, Winders AD, Buell HE, Riggs DB, Lester GE, et al. Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Intern Med 1998;128:186–93.

[14] Haworth CS, Selby PL, Webb AK, Martin L, Elborn JS, Sharples LD, et al. Inflammatory related changes in bone mineral content in adults with cystic fibrosis. Thorax 2004;59:613–7.

[15] Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, et al. Relationship of interleukin-6 and tumor necrosis factor α with muscle mass and muscle strength in elderly men and women: the health ABC study. J Gerontol 2002;57A:M326–32.

[16] Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, et al. Inflammatory response and body composition in COPD. Am J Respir Crit Care Med 2001;164:1414–8.

[17] Flores EA, Bistrian BR, Pomposelli JJ, Dinarello CA, Blackburn GL, Istfan NW. Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. J Clin Invest 1989;83:1614–22.

[18] Tiao G, Hoblet S, Wang JJ, Meyer TA, Luchette FA, Fischer JE, et al. Sepsis is associated with increased mRNAs of the ubiquitin proteasome proteolytic pathway in human skeletal muscle. J Clin Invest 1997;99:163–8.

[19] Cotes JE. Lung function—assessment and application in medicine. Blackwell Scientific Publications.

[20] McArdle WD, Katch FI, Katch VL. Exercise physiology—Energy, nutrition and human performance. Lippincott Williams and Wilkins. p. 159.

[21] Wilson PWF, Paffenbarger PS, Morris JN, Havlik RJ. Assessment methods for physical activity and physical fitness in population

studies: report from NHLBI workshop. Am Heart J 1986;111: 1177–92.
[22] Palange P, Forte S, Felli A, Galassetti P, Serra P, Carlone S. Nutritional state and exercise tolerance in patients with COPD. Chest 1995; 107:1206–12.
[23] Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol 1984; 56:831–8.
[24] Engelen MPKJ, Schols AMWJ, Does JD, Deutz NEP, Wouters EFM. Exercise-induced lactate increase in relation to muscle substrates in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162:1697–704.
[25] Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol 1999;515:287–91.
[26] Vassilakopoulos T, Zakynthinos S, Roussos C. Strenuous resistive breathing induces proinflammatory cytokines and stimulates the HPA axis in humans. Am J Physiol 1999 (Oct.);277(4 Pt 2):R1013–9.
[27] Pedersen M, Bruunsgaard H, Weis N, Hendel HW, Andreassen BU, Eldrup E, et al. Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. Mech Ageing Dev 2003;124:495–502.
[28] Roubenoff R, Harris TB, Abad LW, Wilson PW, Dallal GE, Dinarello CA. Monocyte cytokine production in an elderly population: effect of age and inflammation. J Gerontol, Ser A, Biol Sci Med Sci 1998; 53:M20–6.
[29] Gelato MC, Mynarcik D, McNurlan MA. Soluble tumour necrosis factor alpha receptor 2, a serum marker of resistance to the anabolic actions of growth hormone in subjects with HIV disease. Clin Sci (Lond) 2002 (Jan.);102(1):85–90.
[30] Tsujinaka T, Fujita J, Ebisui C, Yano M, Kominami E, Suzuki K, et al. Interleukin 6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice. J Clin Invest 1996;97:244–9.
[31] Baeza-Raja B, Monoz-Canoves P. p38 MAPK-induced nuclear factor-κB activity is required for skeletal muscle differentiation: role of interleukin-6. Mol Biol Cell 2004;15:2013–26.
[32] Kosmidou I, Vassilakopoulos T, Xagorari A, Zakynthinos S, Papapetropoulos A, Roussos C. Production of interleukin-6 by skeletal myotubes: role of reactive oxygen species. Am J Respir Cell Mol Biol 2002;26(5):587–93.
[33] Chandel NS, Trzyna WC, McClintock DS, Schumacker PT. Role of oxidants in NF-kappa B activation and TNF-alpha gene transcription induced by hypoxia and endotoxin. J Immunol 2000;165: 1013–21.
[34] Jeukendrup AE, Vet-Joop K, Sturk A, Stegen JH, Senden J, Saris WH, et al. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. Clin Sci (Lond) 2000; 98:47–55.
[35] Langen RC, Schols AM, Kelders MC, Wouters EF, Janssen-Heininger YM. Inflammatory cytokines inhibit myogenic differentiation through activation of nuclear factor-kappaB. FASEB J 2001;15:1169–80.
[36] Rabinovich RA, Figueras M, Ardite E, Carbo N, Troosters T, Filella X, et al. Increased tumor necrosis factor-α plasma levels during moderate-intensity exercise in COPD patients. Eur Respir J 2003;21: 789–94.
[37] Greiwe JS, Cheng B, Rubin DC, Yarasheski KE, Semenkovich CF. Resistance exercise decreases skeletal muscle tumour necrosis factor α in frail elderly humans. FASEB J 2001;15:475–82.
[38] Ionescu AA, Mickleborough TD, Bolton CE, Lindley MR, Nixon LS, Dunseath G, et al. Exercise-induced IL-6 and lactate production are increased in adults with cystic fibrosis (CF). Am J Respir Crit Care Med 2004;169:A22.