

Measurement of the acute inflammatory response to walking exercise in COPD: effects of pulmonary rehabilitation

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Objective: This pilot study concerns the evaluation of the acute cytokine response to exercise and changes in this throughout a 7 week pulmonary rehabilitation programme.

Methods: 17 (10 male, 7 female) stable COPD patients, mean (SD) age 69 (8) yrs, mean FEV₁, 51.3 (17.3) % predicted entered into 7 weeks of rehabilitation. The acute cytokine response (ACR) was measured from serum cytokine levels; Interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP) taken pre, post and 1 hour post-maximal incremental shuttle walking test (ISWT). The ACR to maximal exercise was determined before rehabilitation (T0) and post rehabilitation (T7). The ACR (pre/post test) to iso-distance exercise (based on initial ISWT distance) was determined throughout the rehabilitation period at 2 (T2), 4 (T4) weeks and at the end (T7).

Results: 12 patients completed the study. Maximal ISWT distance significantly increased after rehabilitation. There was no significant change in baseline cytokine level throughout; or in pre/post-exercise cytokine levels prior to, during or following rehabilitation.

Conclusions: There was no significant inflammatory response associated with maximal exercise before or after training. Cytokine responses to a fixed bout of exercise did not alter markedly throughout. Clinical PR is unlikely to exacerbate systemic inflammation in COPD.

Keywords: chronic obstructive pulmonary disease, cytokines, exercise

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by fixed airflow obstruction and systemic inflammatory complications. Serum inflammatory markers are elevated in patients with COPD compared with healthy subjects (Gan et al 2004) and catabolic and anabolic imbalances may have deleterious effects on peripheral muscle (Debigare et al 2001). There is increasing evidence to support the premise that inflammation may contribute to impairment in health status and exercise tolerance in patients with COPD (Broekhuizen et al 2006). Exercise as part of pulmonary rehabilitation is a proven beneficial therapy for COPD, improving symptoms and functional outcomes (Lacasse et al 2002). In healthy individuals strenuous exercise has been shown to provoke an inflammatory response with predominant production of anti-inflammatory cytokines interleukin-6 (IL-6), interleukin-1 receptor agonist (IL-1ra) and soluble-tissue necrosis factor receptors (s-TNF-R) (Petersen and Pedersen 2005), whilst pro-inflammatory IL-6 may help to attenuate production of TNF- α (Starkie et al 2003).

Since COPD patients demonstrate increased systemic inflammation at rest (van Helvoort et al 2005), it is theorized that exercise should be carefully prescribed to avoid intensifying the inflammatory state. Early data shows higher TNF- α and IL-6 in CF patients compared with healthy subjects. These differences persisted after moderate

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intensity exercise (Tirakitsoontorn et al 2001). Similarly, COPD patients are de-conditioned and exercise might induce a larger increase in these inflammatory mediators. Rabinovich et al demonstrated a significant increase in TNF- α after 11 minutes of constant work rate cycling exercise in severe COPD patients but not in healthy subjects (Rabinovich et al 2003). Individual cytokine response varies greatly, with intensity and duration of exercise (Petersen and Pedersen 2005) body composition (Schols et al 1996), age and gender (Timmons et al 2006).

The paucity of research available regarding the acute exercise-induced cytokine response in COPD patients makes inferring relationships difficult. A significant reduction in baseline CRP has been demonstrated in healthy marathon runners after 9 months of training compared to untrained controls (Mattusch et al 2000). Greiwe and colleagues reported that following 6 months of resistance training, healthy older subjects had reduced muscle TNF- α , mRNA and protein levels whilst anabolism increased (Greiwe et al 2001). Exercise in healthy subjects clearly confers anti-inflammatory benefits, but whether this also occurs in COPD, is at present unknown.

The purpose of this pilot study was to determine the cytokine response to a maximal walking test, and to determine whether there was any effect of a 7-week training and education programme on the response to fixed walking exercise.

Methods

Patients

Twenty patients with a known diagnosis of COPD were recruited through primary and secondary referral processes. COPD was confirmed with spirometry values consistent with obstructive airways disease (The COPD guidelines group of the standards of care committee of the british thoracic society 1999). Seventeen (10 males, 7 females) COPD patients (aged 55–82 years) with mild to very severe COPD (FEV₁ 94%–27% predicted) according to GOLD criteria (Buist et al 2006), attended for an initial assessment. Six patients were present smokers, 10 patients were ex-smokers and 1 patient was described as a non-smoker, mean (SD) pack years 48.1 (17.8). Twelve (6 male, 6 female) COPD patients (aged 62–82 years) with mild to very severe COPD (FEV₁ 91%–22% predicted) according to GOLD criteria (Buist et al 2006) completed pulmonary rehabilitation and the testing protocol. 3 patients were still smoking, 8 were ex-smokers, and 1 patient was described as a non-smoker. Exclusion criteria consisted of exacerbation necessitating any change in medication or significant worsening of symptoms within the 6 weeks prior to the first assessment, unstable angina or

known cardiac disease, mobility limiting joint problems, known neurological disease and other inflammatory conditions such as rheumatoid arthritis. Medication was unaltered; no patients were receiving oral steroids at the time of the study. Full ethical approval was received from Merton & Sutton/Wandsworth COREC and patients gave informed written consent.

Primary outcomes

Exercise capacity was assessed using the incremental shuttle walk test (ISWT) which is a maximal, standardised, externally paced incremental exercise test (Singh et al 1992). The test involves the patient walking between two cones placed 9 meters apart (hence a distance of 10 m) at a speed externally paced via the use of a tape recording. The speed of shuttles increases each minute until the patient can no longer match the pace or reaches a symptom limiting maximum. The instructions are standardised and delivered via the tape recording. One practice walk was performed a week prior to the ISWT. For safety reasons percutaneous oxygen saturation (SpO₂) and heart rate (HR) were monitored throughout the test and patients were stopped if blood oxygen saturation fell to less than 80% or predicted HR max was reached.

Acute exercise induced cytokine response

The acute exercise induced cytokine response was measured from venous blood collected from the cubital veins before ISWT and immediately post ISWT (T0). A further blood sample was taken after patients rested for 1 hour. Patients then entered a 7 week pulmonary rehabilitation programme. Pre and post ISWT blood tests were repeated using the iso-distance measurements of ISWT (patients were instructed to stop at the level achieved at the initial assessment ISWT) at, 2 weeks (T2) and 4 weeks (T4) into the training period and at 7 weeks (T7), the end of the rehabilitation period.

After rehabilitation (T7) two walking tests were performed 2 days apart: a symptom-limited maximal ISWT and an iso-distance measurement based on the results of the initial walking test. The acute cytokine response was determined for both these walks. At T0 and T7 patients were asked to rest after the walking tests for 1 hour and bloods were taken again to evaluate further post-exercise responses (Figure 1).

The rehabilitation programme

Patients attended outpatient pulmonary rehabilitation, which consisted of exercise and education sessions in accordance with BTS guidelines (Morgan et al 2001), twice weekly

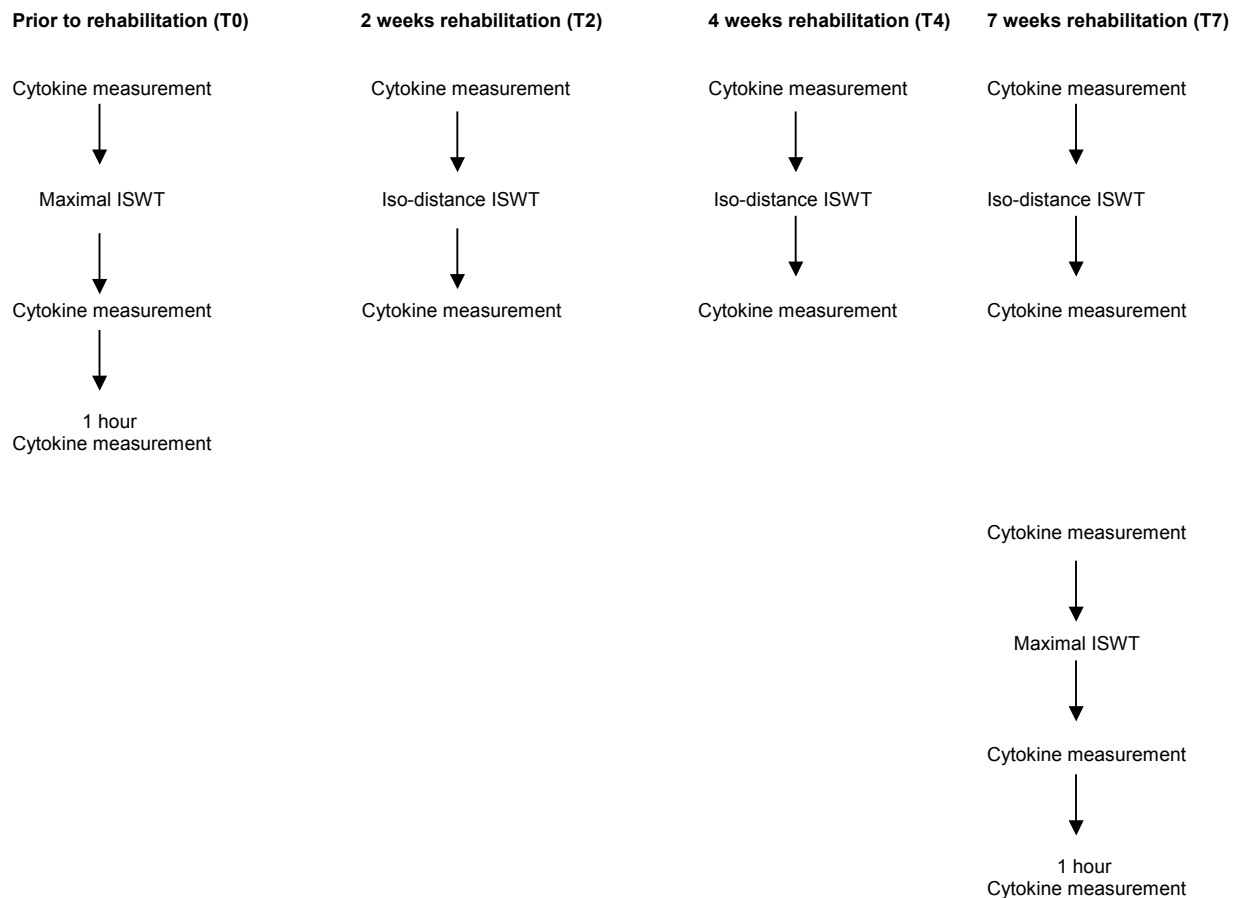


Figure 1 Schematic diagram depicting cytokine measurements and walking tests during pulmonary rehabilitation.

for 7 weeks. If sessions were missed, additional attendance was organized. In addition to this, patients were required to complete 20 minutes of home exercise each day, five times a week. The exercise programme has been previously described (Garrod et al 2004). Each rehabilitation session comprised one hour of exercise followed by an education session. Exercises were a mixture of functional aerobic and resistance activities-walking and cycling, sit to stands, step-ups and upper limb work.

Cytokine measurements

C-reactive protein (CRP) Interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α) were determined from venous blood at the time points described above. Plasma was frozen at -80°C within an hour of sampling. High sensitivity CRP, IL-6 and TNF- α were all measured using commercially available assays (Euro/DPC Ltd, Gwynedd, UK) and performed on an Immulite[®] automated analyser (Euro/DPC Ltd). The functional sensitivities of each of the assays were 0.2 mg/L^{-1} , 2.0 pg/mL^{-1} , and 1.7 pg/mL^{-1} for CRP, IL-6 and TNF- α respectively. The manufacturer claimed within-

assay and between-assay precisions to be less than 8% at the concentrations reported here for all three assays.

Spirometry

Spirometry was performed using a hand held Spirometer (Microloop ML 3535, Micromedical Ltd.). The best of 3 attempts was taken and all researchers were trained in the use of spirometry according to American Thoracic Society guidelines (The COPD guidelines group of the standards of care committee of the British Thoracic Society 1999). Verbal encouragement was standardized for all tests.

Body composition

Percentage body fat was determined using bioelectrical-impedance methods with Tanita scales (Body Composition Analyzer, BC-418MA, Tanita, UK Ltd, The Barn, Philpots Close, Yiewsley, West Drayton, Middlesex, England, UB77RY). Fat mass was calculated using body fat percentage and body weight; fat free mass was calculated by subtracting fat mass from body weight. FFMI was calculated by FM in $\text{kg}/(\text{height in m}^2)$ and nutritional depletion was defined as

BMI ≤ 21 kg.m² and/or FFMI ≤ 15 (females) or ≤ 16 (males) kg.m² (Schols et al 1993).

Quadriceps muscle strength

Quadriceps muscle strength was tested using a hand held Myometer (SH-5001, Physio-Med Services, Glossop Brook Business Park, Surrey Street, Glossop, Derby, SK13 7AJ) with the patient seated and knee at 90° flexion.

Health status

Health status was assessed using the St. George's Respiratory Questionnaire (SGRQ) (Jones et al 1992). This 50 item, disease-specific, self-complete questionnaire has been validated to measure health impairment in respiratory patients. Scores range from 100 'worst possible health status' to 0 'best possible health status.'

Statistical analysis

Pre-exercise TNF- α data at T4 from 1 subject was removed as this subject had an abnormally high result, which was significantly lower at all other time points. The acute exercise induced cytokine response to a fixed bout of exercise (iso-ISWT) throughout the pulmonary rehabilitation programme was calculated by: rest cytokine value-post walk value for T0, T2, T4, T7 and analysis of variance (ANOVA) was used to identify change in this response. These data were normally distributed. Paired t tests were used to identify change in cytokine response to the maximal walking test before and after pulmonary rehabilitation. To identify differences in the plasma level of CRP, IL-6 and TNF- at rest, post and 1 hour post-maximal ISWT at T0 and T7, Friedman's test was used (cytokine data was not normally distributed). Heterogeneity in the acute cytokine response at T0 was explored according to the acute cytokine response. Baseline characteristics for those that dropped out of rehabilitation were compared with those that completed using Mann Whitney un-paired test.

Results

Patient details

Baseline characteristics (Table 1) of the patients who completed rehabilitation (n = 12) compared to those who did not (n = 5) were not significantly different apart from forced vital capacity (FVC) mean difference (95% CI) 1.7 (0.43 to 3.04)l and shuttle walk distance mean difference (95% CI) 197.8 (77.7 to 318.0)m. One female patient suffered from fat free mass depletion (FFMI 13.8kg.m²) and nutritional depletion (BMI 14.5 kg.m²). This female had a reduced CRP and IL-6 concentration pre and post exercise at T0 compared with the

non-depleted group value (median (range) CRP pre: 0.82 vs 3.88 (12.34); CRP post: 0.51 vs 4.2 (13.0); IL-6 pre: 2.1 vs 2.3 (5.0); IL-6 post: 2.1 vs 3.2 (4.3)), whilst at T0, TNF- α pre exercise was similar but post exercise higher (TNF- α pre: 15.0 vs 6.8 (43.2); TNF- α post: 33.0 vs 6.8 (43.2)).

Effects of rehabilitation

As expected there was a statistically significant effect of rehabilitation on maximal ISWT, mean difference (95% CI) 37.5 (10.4 to 64.6) m, although it is not clear how much of an improvement in distance is needed to be clinically significant (The Australian lung foundation and Australian physiotherapy association 2006). However, Quadriceps strength did not change significantly over time (p = 0.24) n/kg, nor did SGRQ Scores (p = 0.43).

Iso-distance cytokine response

Table 2 shows the exercise induced cytokine response at equivalent work load (iso time ISWT) over 7 week rehabilitation period (n = 12). There were no significant differences over time. 8 patients were able to complete iso time ISWT's over the 7 week training period, whilst 3 patients were not able to complete this distance at all times: patient 7 had a reduction of 20 m at 2 and 4 weeks; patient 's10 and 11 had a reduction of 20 m at week 7.

Maximal distance cytokine response

There was no significant difference in the acute cytokine response to a maximal bout of walking pre or post rehabilitation in these patients (Table 3).

One hour post

At the one hour time point after the maximal exercise test, before and upon completion of rehabilitation, there was no significant difference in CRP, IL-6 or TNF- α (data not shown).

Table 1 Patient characteristics

N	12
Male/Female	6 6
Age years	69 (8)
BMI kg.m ⁻²	28.4 (7.2)
FEV ₁ L	1.4 (0.8)
FEV ₁ % predicted	48.9 (19.3)
FFM kg.m ⁻²	23.2 (12.1)
FFMI kg.m ⁻²	20.6 (3.4)
Maximal ISWT distance (m)	234.2 (92)

Data are presented as mean (SD). BMI: body mass index; FEV₁: forced expiratory volume in one second; % predicted: per cent predicted. FFM: fat-free mass index; FFM: Fat mass index; ISWT: incremental shuttle walk test.

Table 2 Exercise induced cytokine response at equivalent work load (iso distance ISWT) over 7 week rehabilitation period (n = 12)

	CRP pre ISWT (mg/l)	CRP post ISWT (mg/l)	IL6 pre ISWT (pg/ml)	IL6 post ISWT (pg/ml)	TNF pre ISWT (pg/ml)	TNF post ISWT (pg/ml)
Week 1	3.8 (12.4)	3.5 (13.1)	2.2 (5.0)	2.6 (1.5)	8.7 (43.2)	7.7 (40.0)
Week 2	2.3 (9.7)	2.8 (10.1)	3.1 (4.9)	2.9 (4.5)	8.4 (31.6)	9.1 (35.8)
Week 4	2.4 (7.6)	2.4 (10.2)	3.6 (4.1)	3.4 (6.5)	8.9 (37.6)	10.0 (36.3)
Week 7	2.6 (9.9)	3.4 (13.1)	3.5 (5.7)	3.9 (6.7)	10.2 (43.0)	9.6 (56.6)

Data presented as median (range)

Heterogeneity in acute cytokine response

There was heterogeneity in the acute cytokine response to a maximal bout of walking between subjects at baseline (Figure 2).

Dropouts compared with those that completed rehabilitation

Those that dropped out of rehabilitation demonstrated a significantly higher walking distance, mean difference (SD); 197.8(56.3) m ($p = <0.05$) and greater FVC; 1.7 (0.6) l ($p = 0.01$) at baseline.

Discussion

The main findings of this study strongly support the view that in response to a maximal bout of walking in COPD patients there is no significant acute cytokine response demonstrated. Although, in this pilot study our sample size is small, we note the large standard deviations for cytokine response and consistency of our results. This suggests that in this population of COPD patients, changes in cytokine levels as a result of maximal walking are likely to be small if present at all. This novel study design enabled us to assess possible change in cytokine response to iso-distance exercise throughout the training period. There was no modification to cytokine levels (or acute changes) over the 7-week period of rehabilitation. There was however, heterogeneity in the exercise induced cytokine response between subjects. A

number of factors are known to influence the acute exercise induced cytokine response including body mass composition (Schols et al 1996), age, gender (Timmons et al 2006), carbohydrate load (Nieman et al 2005) and timing of exercise in relation to previous bouts of activity (Li and Gleeson 2004). Unfortunately in this study we did not standardise for caffeine and carbohydrate ingestion prior to testing. We did however record body composition prior to the testing procedure but there was no significant difference in cytokine release according to percentage body fat. In one female patient, with lean mass and nutritional depletion, TNF- α release after the initial exercise bout was high, compared with the rest of the group who were not depleted. This finding is similar to that of other authors suggesting that muscle status may be an important determinant in the inflammatory response to exercise (Rabinovich et al 2003; van Helvoort et al 2005; van Helvoort et al 2006).

Detailed characterisation of patients prior to these evaluations will be necessary in order to enable us to eventually tease out possible influences on cytokine exercise responses.

In accordance with us, Rabinovich and colleagues recently showed that IL-6 levels remained unchanged in both 6 healthy subjects and 11 COPD patients after exercise (Rabinovich et al 2003). In this study steady state low intensity exercise (40% of maximal) was chosen as the stimulus and sustained for 11 minutes. However, interestingly, TNF- α levels increased significantly from baseline in

Table 3 Acute exercise induced cytokine response (before and after bout of walking) pre and post 7 week rehabilitation period

	Pre rehabilitation	Post rehabilitation	Mean diff (95% CI)	P value
Δ TNF (n = 10) (pg/ml)	3.6 (13.9)	-1.1 (15.5)	-1.1 (-3.7 to 1.5)	0.5
Δ CRP (n = 12) (mg/l)	0.2 (2.1)	1.2 (2.7)	-0.5 (-1.7 to 0.7)	0.4
Δ IL6 (n = 11) (pg/ml)	-0.2 (1.0)	0.3 (1.5)	4.6 (-11.3 to 20.6)	0.4

Mean change calculated resting cytokine – post walk cytokine measure – negative value = rise in cytokine expression
All change data showed normal distribution

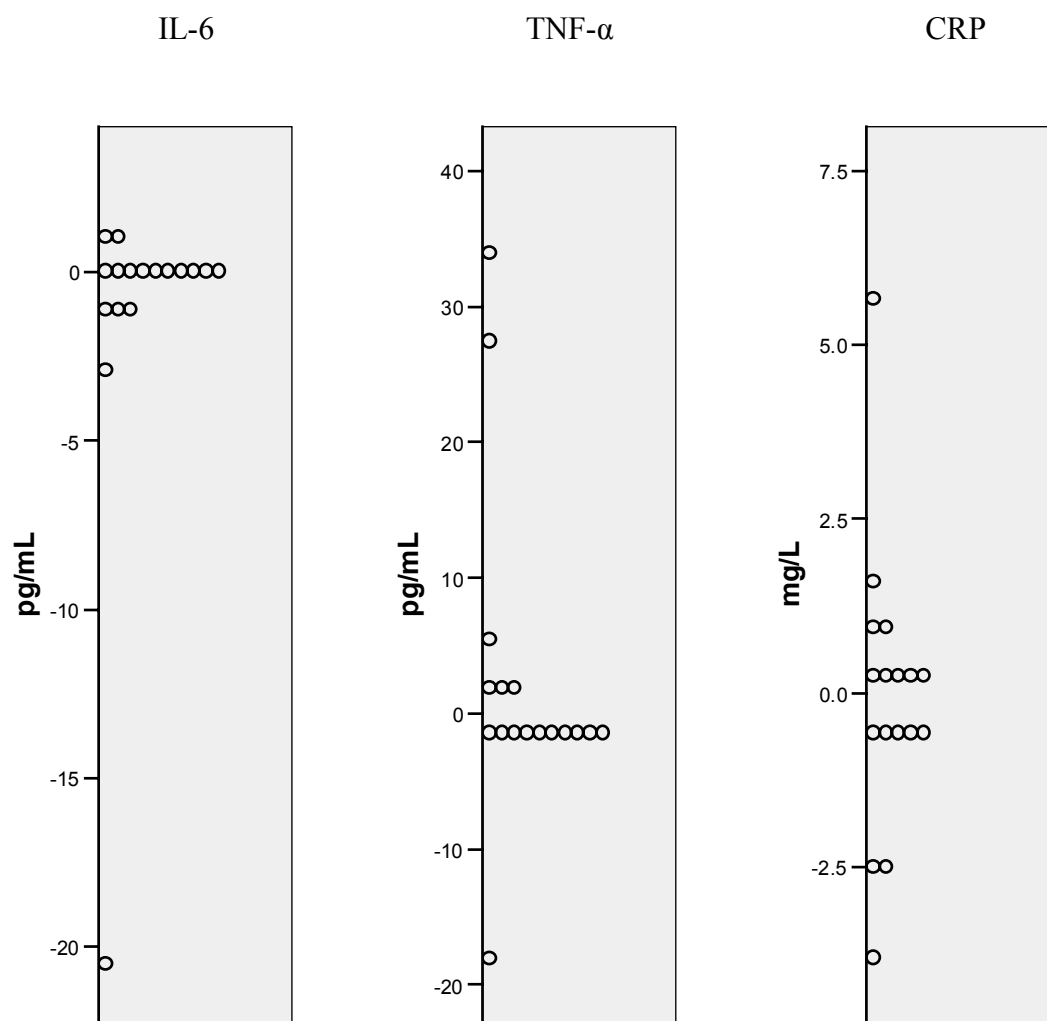


Figure 2 Individual changes (pre-post) in interleukin-6, tumour necrosis factor alpha and C-reactive protein with maximal incremental shuttle walking test before pulmonary rehabilitation.

the COPD patients, even persisting after 8 weeks training, but did not in the healthy controls (Rabinovich et al 2003). We had hypothesised, that as in healthy subjects, IL-6 would prove to attenuate exercise induced TNF- α levels (Starkie et al 2003). However, we found little evidence of this in our study. Body composition was not assessed by Rabinovich and colleagues making comparison with their study difficult. It is feasible that in their study the population were depleted (Rabinovich et al 2003).

Van Helvoort in contrast, tested 16 COPD subjects with maximal incremental cycle ergometry and although circulating lymphocytes were significantly higher after exercise, there were no changes in CRP; whilst IL-6 and TNF- α were not measured (van Helvoort et al 2005). At present we cannot tell whether the exercise induced cytokine response in COPD differs from that of healthy subjects or whether it is merely a reflection of the fact that by necessity exercise intensities are

considerably lower. A criticism of our study is that, unlike these previous studies, we did not include healthy control subjects; we were however predominantly interested in any modifying effects of rehabilitation in this group rather than comparisons.

These data support the now well established view that systemic inflammation is higher in patients with COPD (Gan et al 2004) particularly in muscle-wasted COPD patients, and that acute maximal exercise in non-muscle wasted COPD patients does not cause pronounced cytokine release (van Helvoort et al 2006). There is strong evidence in healthy subjects that CRP levels of higher than 3 mg/L⁻¹ are highly associated with cardiovascular mortality and morbidity (Torres and Ridker 2003). Our hypothesis, that pulmonary rehabilitation may modify pro-inflammatory mediators, as long term training in healthy subjects does (Jankord 2004), has not been demonstrated in this small pilot study. Five out of our 17 patients

were unable to complete rehabilitation, (4 patients suffered an exacerbation and 1 refused after initial assessment). Our patients who dropped out of rehabilitation were able to walk significantly further than those who completed rehabilitation. This limits our study findings since these may be fitter patients who might have been expected to train at a higher intensity and endurance and therefore show a modifying effect of exercise on inflammatory markers. Thus before we conclude a lack of effect of training on inflammation in COPD subjects, further trials would do well to look at longer term training, possibly with increased resistive exercise (Greiwe et al 2001) in patients with mild disease and in larger samples. In conclusion, this study is reassuring in that clinical pulmonary rehabilitation is unlikely to enhance systemic inflammation in non-muscle wasted COPD patients.

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