Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Quadriceps strength and endurance in fibrotic idiopathic interstitial pneumonia

LAURA MENDOZA,[1,3] ATHENA GOGALI,[3] DINESH SHRIKRISHNA,[3] GABRIEL CAVADA,[2] SAMUEL V. KEMP,[3] SAMANTHA A. NATANEK,[3] ABIGAIL S. JACKSON,[3] MICHAEL I. POLKEY,[3] ATHOL U. WELLS[3] AND NICHOLAS S. HOPKINSON[3]

[1]*Hospital Clínico,* [2]*Escuela de Salud Pública, Universidad de Chile, Santiago, Chile, and* [3]*National Institute for Health Research Respiratory Biomedical Research Unit at Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, UK*

ABSTRACT

Background and objective: **Quadriceps muscle dysfunction is an important contributor to exercise limitation in chronic obstructive pulmonary disease, but little is known about skeletal muscle function and its impact on exercise capacity in patients with fibrotic idiopathic interstitial pneumonia (IIP). The aim of the study was to compare quadriceps strength and endurance in patients with fibrotic IIP and healthy controls, and relate it to exercise capacity.**

Methods: **Quadriceps strength and endurance, as well as respiratory muscle strength, and 6-min walk distance were compared among 25 patients with fibrotic IIP, forced vital capacity mean (standard deviation) 78.7 (14.0) %predicted, carbon monoxide transfer factor 40.3 (10.9) %predicted and 33 age-matched healthy controls using non-volitional measures. Quadriceps strength was assessed using magnetic femoral nerve stimulation (quadriceps twitch force), and endurance using the decay in force in response to repetitive magnetic stimulation of the quadriceps over 5 min.**

Results: **Both groups had comparable anthropometrics, gender proportion and respiratory muscle strength. Patients were significantly weaker than controls; quadriceps twitch force 10.1 (3.0) kg versus 8.0 (2.4) kg ($P = 0.013$). Quadriceps force in response to repetitive magnetic stimulation declined significantly more rapidly in patients during the endurance protocol ($P < 0.001$). In controls, there was a significant relationship between 6-min walk distance and quadriceps twitch force (r 0.40, $P = 0.038$), and quadriceps endurance (r 0.59, $P = 0.016$). In patients, only PaO_2 and inspiratory muscle strength were retained as independent correlates of 6-min walk distance ($r^2 = 0.3$ $P = 0.022$).**

Conclusions: **Quadriceps strength and endurance are reduced in patients with fibrotic IIP compared with healthy controls, but are less tightly correlated with exercise performance.**

SUMMARY AT A GLANCE

This study demonstrates that quadriceps strength and endurance are significantly reduced in patients with fibrotic idiopathic interstitial pneumonia compared with healthy controls.

Key words: exercise, interstitial lung disease, magnetic stimulation, muscle, pulmonary fibrosis.

Abbreviations: 6MWT, 6-min walking test; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; SNiP, maximum sniff nasal pressure.

INTRODUCTION

Peripheral muscle dysfunction is a common feature of chronic cardiorespiratory diseases, including chronic obstructive pulmonary disease and heart failure. It is an important factor contributing to exercise limitation in these conditions, can occur early in the course of disease,[1,2] and is associated with a worse quality of life and increased mortality.[3–7] However, few data exist regarding skeletal muscle in patients with interstitial lung disease.[8–10]

Fibrotic idiopathic interstitial pneumonia (IIP) includes two categories of idiopathic pneumonia, which are characterized by a predominance of pulmonary fibrosis and share a similar clinical presentation and prognosis: idiopathic pulmonary fibrosis (IPF) and fibrotic nonspecific interstitial pneumonia.[11,12] Patients with fibrotic IIP experience progressive exertional dyspnoea and reduced exercise capacity, both attributed to pulmonary function deterioration.[13–17] However, it has been demonstrated that some patients with interstitial lung disease report leg fatigue as the symptom limiting their exercise capacity,[18] and Nishiyama *et al.* found a correlation between quadriceps strength and maximum oxygen uptake in patients with IPF,[10] suggesting that locomotor muscle dysfunction may contribute to exercise

Correspondence: Laura Mendoza, Hospital Clínico Universidad de Chile, Santos Dumont 999, Independencia, Santiago, Chile. Email: lmendoza08@gmail.com

Received 4 June 2013; invited to revise 4 July 2013; revised 16 July 2013; accepted 3 August 2013 (Associate Editor: Amanda Piper).

limitation. Moreover, pulmonary rehabilitation, a treatment modality that does not influence lung function, improves functional capacity in patients with IPF,[19–21] although the benefits in the limited studies that have been done to date seem to be of shorter duration than those observed in other populations.[22] We hypothesized that there is significant quadriceps dysfunction in patients with fibrotic IIP, which could also be a contributing factor to exercise limitation.

Muscle function includes strength, the maximum force that can be generated, and endurance, the ability to sustain a given load. Volitional measures of both of these may be influenced by coordination or motivation, so the aim of the present study was to determine whether quadriceps strength and endurance are reduced in patients with fibrotic IIP using both volitional and non-volitional techniques involving magnetic nerve stimulation.[23] Some of the data have been presented previously in abstract form.[24]

METHODS

Study population

This prospective, cohort study enrolled patients with a clinical diagnosis of IPF or fibrotic nonspecific interstitial pneumonia[25,26] attending the interstitial lung disease clinic at Royal Brompton Hospital between December 2008 and July 2009. Diagnosis was based on clinical features that included computed tomography scan appearances, supported in some cases by histology. Exclusions were significant comorbidity likely to limit exercise capacity, a cardiac pacemaker (which contraindicates magnetic stimulation) or an inability to perform a 6-min walking test (6MWT). Healthy age-matched controls were recruited from the local community by advertisement. The Royal Brompton, Harefield and National Heart and Lung Institute Research Ethics Committee approved the study. Participants provided written informed consent.

Study protocol

Quadriceps maximum voluntary contraction force was measured with subjects lying supine, their knee flexed at 90° over the end of the bed.[27,28] The force generated was visible to subjects on screen, and they received vigorous encouragement to achieve a maximum effort. At least three attempts were made, with further repetitions until there was no increase in the force generated. Quadriceps maximum voluntary contraction force was expressed as the percentage of predicted value (corrected for fat-free mass, age, height and gender).[29]

As a non-volitional measure of quadriceps strength, unpotentiated twitch tension (quadriceps twitch force) was obtained using supramaximal magnetic stimulation of the femoral nerve.[30] Stimuli were delivered after 20-min rest to avoid muscle potentiation. The mean of the best five supramaximal stimulations was selected.

Quadriceps endurance was measured using the repetitive magnetic stimulation technique recently described in detail by Swallow *et al*.[23] A Magstim Rapid[2] device and a flexible mat coil wrapped over the body of the quadriceps were used to stimulate intramuscular branches of the femoral nerve. Two-second 'trains' of stimuli were delivered at 30 Hz with a 3-s gap between each one, giving a duty cycle of 0.4. After adjusting the intensity of stimulation, so that the initial train of stimuli would generate a quadriceps contraction equal to 20% of quadriceps maximum voluntary contraction force, 60 trains were delivered over 5 min and the decay in force plotted as an index of endurance.

Spirometry was performed in all subjects, and carbon monoxide gas transfer, plethysmographic lung volumes (CompactLab, Jaeger, Würzburg, Germany) and blood gas tensions were also measured in patients. Fat-free mass was measured using bioelectrical impedance (Bodystat, QuadScan 4000, Douglas, UK). Clinical history was recorded, including duration of disease and medication, so that the average daily dose prednisone over the preceding 6 months could be calculated.

To assess respiratory muscle strength, maximum sniff nasal pressure (SNiP), inspiratory pressure and expiratory pressures were also determined as previously described.[28]

A 6MWT was used to measure exercise capacity and was performed as the final test of the session, after 30 min of rest according to the American Thoracic Society/ European Respiratory Society guidelines.

Statistical analysis

Results are presented as mean (standard deviation) or median (interquartile range). To compare differences between groups, independent *t* tests were used for continuous variables, the Mann–Whitney test for non-normal data and Fisher's exact test for categorical variables. To compare the endurance curve measurements, we used the following model: Force = $100^{(-b*\text{train})}$, this response was transformed in Y = log(Force/100) and estimated by mixed models without constant. The interaction between train and group was included in the model to compare groups. Pearson's correlation and stepwise linear regression analyses were used to find an association between dependent and independent variables. Because quadriceps endurance could not be measured in all patients, separate regression analyses were performed in this subgroup where appropriate. A significance level of 5% was used. Analysis used SPSS software (SPSS Inc., 1989–2005, Chicago, IL, USA) and STATA (College Station, TX, USA) release 10.1.

RESULTS

Study participants

Twenty-five patients with fibrotic IIP and 33 controls were enrolled in the study. They were comparable in age, gender, anthropometrics and body composition (Table 1). The diagnosis was IPF in 15 cases (surgical biopsy ($n = 6$; clinical/high-resolution computed tomography (HRCT) diagnosis, $n = 9$), fibrotic nonspecific interstitial pneumonia in two cases (both

Table 1 Characteristics of control subjects and patients

	Control subjects (n = 33)	Patients (n = 25)	P-value
Age, year	64.9 (9.4)	64.4 (7.7)	0.84
Sex, M/F	24/9	23/2	0.09
Smoking history			0.035*
Current	8	2	
Ex-smoker	10	16	
Never smoker	15	7	
Pack-years smoked	10.5 (16.8)	26.4 (25.9)	0.006*
BMI, kg/m^2	26.8 (4.2)	28.6 (4.7)	0.21
FFM, kg	56.3 (11.5)	59.5 (10.3)	0.26
% Fat	29.0 (7.0)	30.5 (5.4)	0.37
FEV_1, % predicted	101.5 (14.0)	79.9 (13.9)	<0.001*
FVC, % predicted	106.6 (16.2)	78.7 (14.0)	<0.001*
FEV_1/FVC %	75.9 (5.0)	78.0 (5.6)	0.13
TLC, % predicted	—	68.7 ± 10.2	—
RV/TLC, % predicted	—	32.3 ± 3.7	—
DLco, % predicted	—	40.3 ± 10.9	—
PaO_2, kPa	—	9.9 ± 1.1	—
$PaCO_2$ kPa	—	5.1 ± 0.39	—
SNiP, cm H_2O	97.9 (27.8)	96.3 (32.3)	0.50
PImax, cm H_2O	90.0 (30.8)	97.1 (35.1)	0.67
PEmax, cm H_2O	95.6 (31.2)	108.8 (35.6)	0.58
QMVC, %pred	65.0 (16.3)	60.5 (16.5)	0.29
TwQ, Kg	10.1 (3.0)	8.0 (2.4)	0.013*

*P < 0.05 values are mean (standard deviation).

% Fat, percentage body fat; BMI, body mass index; DLco, carbon monoxide transfer factor; FEV_1, forced expiratory volume in 1 s; FFM, fat-free mass; FVC, forced vital capacity; PaO_2, partial pressure of oxygen breathing air; PEmax maximum expiratory pressure; PImax, maximum inspiratory pressure; QMVC, quadriceps maximum voluntary contraction; RV, residual volume; SNiP, maximum sniff nasal pressure; TLC, total lung capacity; TwQ, quadriceps twitch force in response to magnetic femoral nerve stimulation.

biopsied) and in eight non-biopsied cases; the HRCT appearances were intermediate between IPF and fibrotic nonspecific interstitial pneumonia, with no differential diagnosis thought to be plausible. The average time since disease onset was 3.4 (2.0) years and the average daily dose prednisone in the preceding 6 months was 8.6 (8.5) mg/day. Two patients used oxygen during the walking test. Thirteen had one or more comorbidities, including hypertension (six patients), hypercholesterolaemia (four patients) and diabetes mellitus (three patients).

Muscle function

Quadriceps strength (quadriceps twitch force) was significantly lower in patients 8.0 (2.4) kg versus 10.1 (3.0) kg (P = 0.013) (Fig. 1; Table 1). Respiratory muscle strength did not differ significantly between patients and controls.

Quadriceps endurance was assessed in 19 patients and 16 control subjects. In the remaining participants, it was not possible to obtain an initial response equal to 20% of the quadriceps maximum voluntary

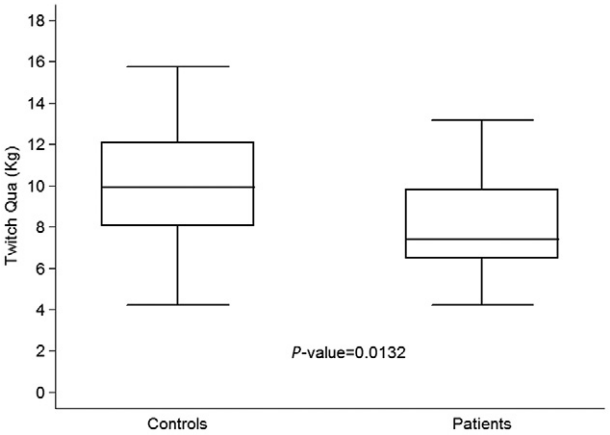

Figure 1 Twitch quadriceps force in patients and controls. Box represents 25th and 75th centiles, and whiskers 90th and 10th centiles.

contraction force required for the fatiguing protocol. This was probably due to obesity and thigh shape, which prevented adequate coil position around the thigh. Decline in quadriceps force by train is shown in Figure 2. The curves differed significantly (P < 0.001) and had the following estimated expressions: force = $100^{(-0.0108 * \text{train})}$ in controls and force = $100^{(-0.0132 * \text{train})}$ in patients. The time to decay to 70% of baseline force (T_{70}) was significantly shorter in the patient group (115 (102.5–135) vs 90 (75–112.5) s, P = 0.038). In control subjects, T_{70} fell with age (r^2 0.26 P = 0.04), increasing percentage body fat (r^2 0.27 P = 0.04) and was significantly correlated with SNiP (r^2 0.26 P = 0.04). In patients, T_{70} was not associated with any demographic or anthropometric factor, lung function, arterial blood gases, average daily dose of prednisone, or disease duration.

Factors influencing exercise capacity

For the 6MWT, patients had lower resting oxygen saturations, a greater degree of desaturation during exercise, and reported a greater increase in leg discomfort and breathlessness than controls, as expected. The distance walked was, on average, 128 m less in patients (Table 2). In the control group, there was a significant association between 6-min walk distance and age, pack years smoked, body mass index, percentage body fat, SNiP, and quadriceps strength and endurance (Table 3). By stepwise regression analysis, including parameters with a P < 0.2 in univariate analysis, only quadriceps strength was retained in the whole control group as a significant correlate of exercise capacity (r^2 0.3 P = 0.001), and only quadriceps endurance (T_{70}) was retained in the 15 controls where this had been measured (r^2 0.35 P = 0.016). In patients, the 6-min walk distance was associated with SNiP, PaO_2 and quadriceps strength but not with quadriceps endurance or with other pulmonary function parameters, including gas transfer in univariate analysis (Table S1). By stepwise analysis, only PaO_2 and SNiP were retained; 6-min walk distance = 86.3 + 1.01(SNiP cmH_2O) + 32.2(PaO_2 kPa) (r^2 = 0.3).

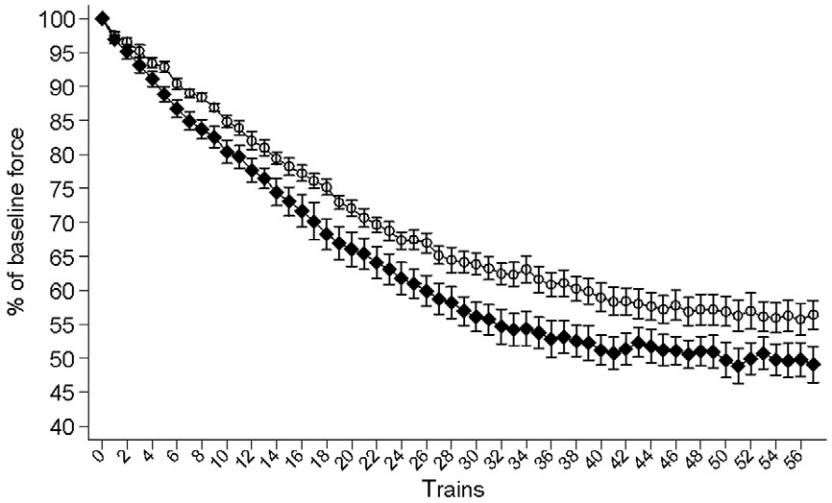

Figure 2 Force declined significantly more rapidly during the repetitive magnetic stimulation protocol in patients $n = 19$ (solid diamonds) than controls $n = 16$ (hollow circles) ($P < 0.001$). Error bars represent standard error of the mean.

Table 2 Six-minute walk parameters in control subjects and patients

	Control subjects	Patients	*P*-value
Resting SaO_2%	97.2 (1.1)	95.0 (1.9)	<0.001
Δ SaO_2%	–0.6 (1.4)	–9.8 (6.6)	<0.001
Δ Breathlessness, Borg score	1.7 (1.3)	2.9 (1.5)	0.006†
Δ Leg fatigue, Borg score	1.5 (1.3)	2.7 (2.2)	0.041†
Distance, m	617.2 (74.6)	489.4 (88.8)	<0.001

Values, except breathlessness and leg fatigue scores, are mean ± standard deviation.

†Mann–Whitney test.

Table 3 Relationship between 6-min walking distance and other variables in control subjects

	R	*P*
Age, year	–0.35	0.049*
Pack-years index	–0.37	0.035*
BMI, kg/m^2	–0.37	0.035*
FFM, kg	–0.05	0.779
% Fat	–0.39	0.026*
SNiP, cm H_2O	0.44	0.028*
QMVC, %predicted	0.55	0.001*
TwQ, Kg	0.40	0.038*
T_{70}, s ($n = 16$)	0.59	0.016*

*$P < 0.05$.

% Fat, percentage body fat; BMI, body mass index; FFM, fat-free mass; QMVC, quadriceps maximum voluntary contraction; SNiP, maximum sniff nasal pressure; T_{70}, time for the force to fall to 70% of baseline force at the repetitive magnetic stimulation protocol; TwQ, quadriceps twitch force.

DISCUSSION

The main finding of this study was that quadriceps strength and endurance were reduced in patients with fibrotic IIP when compared with controls. This finding was particularly robust because of the use of non-volitional measures to assess both these parameters. In control subjects, there was an association between quadriceps function and 6-min walk distance, whereas in patients, 6-min walk distance was independently associated with hypoxia and inspiratory muscle strength but not with quadriceps parameters.

Our study adds to the limited data addressing skeletal muscle weakness in patients with interstitial lung disease.[8–10] Nishiyama *et al.* used voluntary quadriceps force in 41 patients with IPF, and found it to be reduced and associated with performance on cycle ergometry.[10] A key aim of this study was to determine if quadriceps fatigability was a complication in fibrotic IIP. It is interesting to note that the reduction in skeletal muscle endurance in patients was not related to hypoxia, disease duration or use of prednisone. Corticosteroid excess is associated with muscle weakness and although corticosteroid treatment has been proposed as a significant cause of skeletal muscle weakness in chronic obstructive pulmonary disease, although this has not been confirmed,[28,31] and the present data do not suggest that corticosteroid doses used in these patients have a significant effect either. Spruit *et al.* reported an association between corticosteroid exposure and quadriceps peak torque in patients with sarcoidosis.[8]

Although this relationship is plausible, caution is needed since steroid exposure will also be a marker of disease severity, and intramuscular granulomas are commonly seen in sarcoid patients.[32]

The main factor driving skeletal muscle dysfunction, since disease severity markers do not appear relevant, may therefore be reduced physical activity rather than systemic factors. However, as no direct measurements of physical activity were made, this can only be raised as a hypothesis. Of note, quadriceps weakness is also a feature of severe scoliosis, a restrictive extrapulmonary disease in which lung

inflammation is not present and corticosteroid or other systemic treatments are not administered, where it is associated with oxidative stress and fibre type changes similar to those observed in chronic obstructive pulmonary disease.[33]

Respiratory muscle function was preserved in the patient group in this study, as has been previously described in both interstitial lung disease[34] and in chronic obstructive pulmonary disease when a correction is made for lung volume.[35] This could support the concept that quadriceps muscle dysfunction is a common complication of a range of chronic conditions, related largely to the local[29] pattern of use or disuse.

A strength of this study is that quadriceps function was measured using non-volitional techniques. By measuring both volitional and non-volitional quadriceps muscle strength, together with studying the fatigability of the quadriceps muscle using an endurance protocol, we were able to obtain a more complete picture of quadriceps function than in previously published studies where only non-volitional measures were taken.[8,10]

We used the 6MWT instead of a formal cardiopulmonary exercise test to determine exercise capacity. The 6MWT is a well-validated tool of exercise capacity in patients with pulmonary fibrosis.[11,36,37] Only a single 6MWT was performed, but the patients in this study had experience with the 6MWT because it is part of the routine clinical evaluation for interstitial lung disease patients in our institution, so any possible learning effect is likely to have been minimal. Of note, the value of the SaO_2 at the end of the walking test in our patient group was 85%, which is similar to that achieved with exercise testing in previous studies conducted in patients with interstitial lung disease.[10,14]

A further potential issue is that the pulmonary disease might have been associated with a connective tissue disease that could have impacted directly on muscle function. We think that this is unlikely, as patients were recruited having already undergone a clinical evaluation, including history and examination and serological tests to exclude these conditions.

In conclusion, the present study demonstrates that quadriceps endurance and strength are compromised in fibrotic IIP, and this impairment may present a therapeutic target, although possibly one of less importance than in other respiratory conditions such as chronic obstructive pulmonary disease. Further studies, including the analysis of muscle biopsy parameters, are required to identify the contributing factors and mechanisms.

Acknowledgements

We would like to thank Derek Cramer and his staff in the Lung Function Department of The Royal Brompton Hospital for their assistance, and the patients and control subjects for giving their time to participate in the study. L Mendoza was funded by a grant from the Chilean National Scholarship Program for Graduate Studies. The research was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, which also part funds Professor Polkey. Abigail Jackson was supported by The Moulton Medical Foundation, and Dinesh Shrikrishna by The UK Medical Research Council.

REFERENCES

1 Kelly JL, Elkin SL, Fluxman J *et al*. Breathlessness and skeletal muscle weakness in patients undergoing lung health screening in primary care. *COPD* 2013; **10**: 40–54.
2 Shrikrishna D, Patel M, Tanner RJ *et al*. Quadriceps wasting and physical inactivity in patients with COPD. *Eur. Respir. J.* 2012; **40**: 1115–22.
3 Gosker HR, Lencer NHMK, Franssen FME *et al*. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest* 2003; **123**: 1416–24.
4 Hülsmann M, Quittan M, Berger R *et al*. Muscle strength as a predictor of long-term survival in severe congestive heart failure. *Eur. J. Heart Fail.* 2004; **6**: 101–7.
5 Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am. J. Respir. Crit. Care Med.* 1996; **153**: 976–80.
6 Swallow EB, Reyes D, Hopkinson NS *et al*. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007; **62**: 115–20.
7 Shrikrishna D, Hopkinson NS. Chronic obstructive pulmonary disease: consequences beyond the lung. *Clin. Med.* 2012; **12**: 71–4.
8 Spruit MA, Thomeer MJ, Gosselink R *et al*. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005; **60**: 32–8.
9 Hamilton AL, Killian KJ, Summers E *et al*. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am. J. Respir. Crit. Care Med.* 1995; **152**: 2021–31.
10 Nishiyama O, Taniguchi H, Kondoh Y *et al*. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest* 2005; **127**: 2028–33.
11 Eaton T, Young P, Milne D *et al*. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. *Am. J. Respir. Crit. Care Med.* 2005; **171**: 1150–7.
12 Latsi PI, du Bois RM, Nicholson AG *et al*. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am. J. Respir. Crit. Care Med.* 2003; **168**: 531–7.
13 Marciniuk DD, Watts RE, Gallagher CG. Dead space loading and exercise limitation in patients with interstitial lung disease. *Chest* 1994; **105**: 183–9.
14 Harris-Eze AO, Sridhar G, Clemens RE *et al*. Role of hypoxemia and pulmonary mechanics in exercise limitation in interstitial lung disease. *Am. J. Respir. Crit. Care Med.* 1996; **154**: 994–1001.
15 Chetta A, Marangio E, Olivieri D. Pulmonary function testing in interstitial lung diseases. *Respiration* 2004; **71**: 209–13.
16 Burdon JG, Killian KJ, Jones NL. Pattern of breathing during exercise in patients with interstitial lung disease. *Thorax* 1983; **38**: 778–84.
17 Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest* 1996; **109**: 1566–76.
18 Marciniuk DD, Sridhar G, Clemens RE *et al*. Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. *J. Appl. Physiol.* 1994; **77**: 963–73.
19 Naji NA, Connor MC, Donnelly SC *et al*. Effectiveness of pulmonary rehabilitation in restrictive lung disease. *J. Cardiopulm. Rehabil.* 2006; **26**: 237–43.
20 Nishiyama O, Kondoh Y, Kimura T *et al*. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008; **13**: 394–9.
21 Ferreira A, Garvey C, Connors GL *et al*. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. *Chest* 2009; **135**: 442–7.

22 Holland AE, Hill CJ, Conron M *et al*. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax* 2008; **63**: 549–54.
23 Swallow EB, Gosker HR, Ward KA *et al*. A novel technique for nonvolitional assessment of quadriceps muscle endurance in humans. *J. Appl. Physiol.* 2007; **103**: 739–46.
24 Mendoza L, Gogali A, Shrikrishna D *et al*. Quadriceps endurance is reduced in fibrotic idiopathic interstitial pneumonia. *Thorax* 2009; **64**(Suppl. IV): A44–A5.
25 Bradley B, Branley HM, Egan JJ *et al*. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; **63**(Suppl. 5): v1–58.
26 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am. J. Respir. Crit. Care Med.* 2002; **165**: 277–304.
27 Edwards RH, Young A, Hosking GP *et al*. Human skeletal muscle function: description of tests and normal values. *Clin. Sci. Mol. Med.* 1977; **52**: 283–90.
28 Hopkinson NS, Nickol AH, Payne J *et al*. Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2004; **170**: 395–9.
29 Seymour JM, Spruit MA, Hopkinson NS *et al*. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur. Respir. J.* 2010; **36**: 81–8.
30 Polkey MI, Kyroussis D, Hamnegard CH *et al*. Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man. *Muscle Nerve* 1996; **19**: 549–55.
31 Hopkinson NS, Man WD, Dayer MJ *et al*. Acute effect of oral steroids on muscle function in chronic obstructive pulmonary disease. *Eur. Respir. J.* 2004; **24**: 137–42.
32 Andonopoulos AP, Papadimitriou C, Melachrinou M *et al*. Asymptomatic gastrocnemius muscle biopsy: an extremely sensitive and specific test in the pathologic confirmation of sarcoidosis presenting with hilar adenopathy. *Clin. Exp. Rheumatol.* 2001; **19**: 569–72.
33 Swallow EB, Barreiro E, Gosker H *et al*. Quadriceps muscle strength in scoliosis. *Eur. Respir. J.* 2009; **34**: 1429–35.
34 de Troyer A, Yernault JC. Inspiratory muscle force in normal subjects and patients with interstitial lung disease. *Thorax* 1980; **35**: 92–100.
35 Man WD, Soliman MG, Nikoletou D *et al*. Non-volitional assessment of skeletal muscle strength in patients with chronic obstructive pulmonary disease. *Thorax* 2003; **58**: 665–9.
36 Flaherty KR, Andrei AC, Murray S *et al*. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. *Am. J. Respir. Crit. Care Med.* 2006; **174**: 803–9.
37 du Bois RM, Weycker D, Albera C *et al*. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am. J. Respir. Crit. Care Med.* 2011; **183**: 1231–7.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Relationship between 6-min walking distance and other variables in patients