CHAPTER 21

Rehabilitation programmes in sarcoidosis: a multidisciplinary approach

M.A. Spruit[*], E.F.M. Wouters*[#], R. Gosselink*[*]

[*]Dept of Rehabilitation Sciences, Faculty of Kinesiology and Rehabilitation Sciences, Katholieke Universiteit Leuven and Respiratory Rehabilitation, University Hospital Gasthuisberg, Leuven, Belgium. [#]Dept of Respiratory Medicine, University Hospital Maastricht, Maastricht, The Netherlands.

Correspondence: R. Gosselink, Universitair Ziekenhuis Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. Fax: 32 16347126; E-mail: Rik.Gosselink@uz.kuleuven.ac.be

Patients with sarcoidosis suffer from a broad range of persistent symptoms, such as fatigue, dyspnoea and general weakness [1]. To date, specific nonpharmacological treatments to reduce the aforementioned symptoms are mostly lacking in the management of patients with sarcoidosis. Nevertheless, exercise training has shown to improve health status, exercise capacity, skeletal muscle function and complaints of fatigue and dyspnoea in patients with chronic pulmonary or cardiac diseases [2, 3]. The present chapter will provide a rationale for nonpharmacological treatments in patients with sarcoidosis with persistent clinical symptoms.

Sarcoidosis-related symptoms

Fatigue

Although fatigue is clinically difficult to quantify, qualify, and to treat, it has been widely accepted as a highly prevalent and disabling clinical feature in patients with sarcoidosis [4–6]. Recently, 73% of the outpatients with sarcoidosis had a score of >22 points on the Fatigue Assessment Scale (FAS) [4], indicating that a majority of the patients had self-reported complaints of fatigue. Although the determination of the cut-off score is questionable (*e.g.* the cut-off score was set at percentile 80 of the scores obtained in two samples of healthy controls), the cross-sectional study of De Vries *et al.* [4] showed that a score of >22 points on the FAS was independent of an impaired pulmonary function, the treatment of prednisone, and of the circulating levels of soluble interleukin 2 receptor and amyloid A. Other possible underlying causes may, therefore, be responsible for this observed high prevalence of fatigue. In fact, fatigue has been related to muscle dysfunction. Respiratory muscle weakness, as well as skeletal muscle weakness, was positively related to complaints of fatigue [6, 7]. It will, however, be difficult to ascertain which is the chicken and which is the egg in this situation. In addition, the possible role of endocrinological disturbances in the development and/or maintenance of complaints of fatigue have never been studied in patients with sarcoidosis. Nevertheless, male patients with sarcoidosis appear to have reduced circulating levels of testosterone [8], which has been known to be related to complaints of fatigue in other chronic diseases [9, 10].

Eur Respir Mon, 2005, 32, 316–326. European Respiratory Monograph; ISSN 1025-448x. ISBN 1-904097-22-7.

Dyspnoea

A majority of outpatients with sarcoidosis experience dyspnoea during activities of daily living. In a cross-sectional study, 39% of the patients experienced dyspnoea while walking at a rapid pace on level ground, 19% while walking at their own pace on level ground and 14% at rest [11]. Although forced vital capacity and transfer factor of the lung for carbon monoxide were significantly lower than those of healthy control subjects, they did not correlate with the severity of perceived dyspnoea [11]. Low respiratory muscle strength, however, was related to worse scores for dyspnoea on the modified British Medical Research Council scale [11]. Unfortunately, the relationship between skeletal muscle dysfunction and the degree of dyspnoea experienced during day-to-day activities has never been studied in patients with sarcoidosis. Nonetheless, reduction in the strength of the inspiratory muscles [6, 7, 11] may contribute substantially to the intensity of dyspnoea during day-to-day activities. Moreover, physical deconditioning [7], inefficient ventilation and a reduced arterial oxygen tension [12–14] may also contribute to an increased sense of dyspnoea in rest and during exercise.

Pain

Less is known about the prevalence of pain in patients with sarcoidosis. Recently, however, the presence of pain has been evaluated in a cohort of 821 Dutch patients with sarcoidosis. Pain was reported in 72% of the patients, and could be divided in arthralgia (54%), muscle pain (40%), headache (28%) and chest pain (27%) [15]. The data were not compared with a healthy population, so the real prevalence of pain in sarcoidosis currently remains unknown. Nevertheless, pain appeared to be a substantial problem in sarcoidosis and the number of types of pain a patient with sarcoidosis was suffering from (ranging 0–5) was found to be related to a lower quality of life [15]. In addition, lower (worse) scores on the Medical Short Form-36 section "pain" have been related positively to quadriceps muscle weakness in patients with sarcoidosis who spontaneously complained of fatigue at the outpatient consultation [7]. This is in line with the fact that the variation in the number of types of pain could partially be explained by less energy and by the presence of feeling tired [15]. Therefore, in developing the most appropriate therapeutic approach, including rehabilitation programmes, the possible impact of pain, pain behaviour and coping strategies should be well thought-out beside all other relevant aspects of the disease.

Respiratory muscle weakness

Respiratory muscle weakness has been found in patients with sarcoidosis as compared with age-matched healthy controls (fig. 1) [6, 7, 11, 16]. Reduced inspiratory mouth pressure may be due to granulomatous involvement of the main inspiratory muscle (*e.g.* the diaphragm) [17, 18]. Moreover, the pharmacological treatment with oral corticosteroids may affect respiratory muscle function in patients with sarcoidosis, as seen previously in patients with chronic obstructive pulmonary disease [19]. Nevertheless, no significant differences were found in maximal inspiratory mouth pressure between patients who received oral corticosteroids in the 6-month period preceding the tests (76±21% predicted) and those who did not (82±21% predicted, p=0.52) [7]. WIRNSBERGER *et al.* [6] reported similar data. In addition, patients who had used corticosteroids previously, and at the time of assessment, had significantly better maximal inspiratory mouth pressure than those patients who did not (p=0.027) [20]. To date, no biopsies have been taken from the respiratory muscles of patients with sarcoidosis to elucidate the

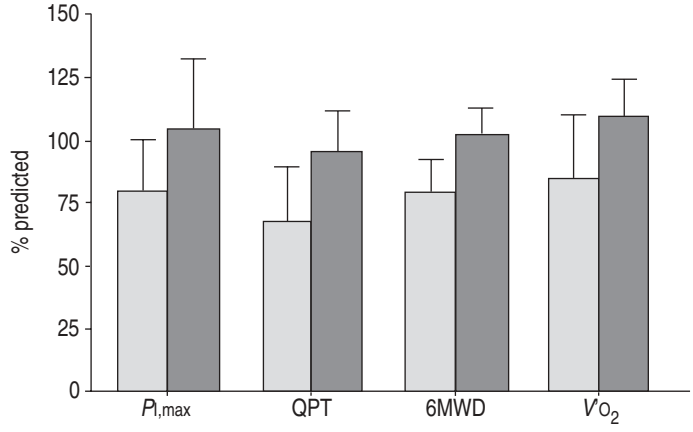

Fig. 1. – Peak inspiratory mouth pressure ($P_{I,max}$), isometric quadriceps femoral muscle peak torque (QPT), the distance walked in 6 minutes (6MWD) and peak oxygen uptake ($V'O_2$) in the patients with sarcoidosis (□) and the healthy control subjects (■). Data obtained from [7].

possible underlying mechanisms of respiratory muscle weakness. Moreover, respiratory muscle function has never been assessed by using magnetic stimulation of the phrenic nerve [21]. Therefore, the possible contamination of the results of the respiratory muscle force test by motivation of patients with sarcoidosis cannot be excluded.

Respiratory muscle endurance has also been shown to be reduced in patients with sarcoidosis as compared with healthy control subjects and to be related to the categories "mobility", "body care" and "movement" of the Sickness Impact Profile (SIP) questionnaire [6]. These SIP categories, however, did not differ between patients with sarcoidosis and the healthy control subjects. Therefore, the clinical relevance of the aforementioned significant relationships needs to be determined.

Skeletal muscle weakness

Skeletal muscle weakness is assumed to be present in patients with sarcoidosis [22]. However, to date only two cross-sectional trials have investigated the presence of skeletal muscle weakness (*i.e.* isometric quadriceps peak torque and isometric handgrip force). WIRNSBERGER *et al.* [6] were the first to study skeletal muscle force in outpatients with sarcoidosis. They did not find significant differences in skeletal muscle force between patients with sarcoidosis and healthy control subjects. In contrast, SPRUIT *et al.* [7] did find a significant difference in quadriceps peak torque and handgrip force between outpatients with sarcoidosis and healthy control subjects (fig. 1) [7]. Although a type II error cannot be excluded in the former study [6], the different results between the two studies are probably due to the fact that only about 35% of the patients studied by WIRNSBERGER *et al.* [6] had self-reported complaints of fatigue, while all patients in the study by SPRUIT *et al.* [7] reported complaints of fatigue. In fact, sarcoidosis patients with self-reported complaints of fatigue had more pronounced respiratory muscle weakness [6], a lower fat-free mass over body weight ratio, and reported more frequently exercise intolerance and muscle pain compared with sarcoidosis patients without fatigue [5]. Fatigue may, therefore, be interrelated with indices of physical deconditioning. If this opens avenues for new therapeutic options, it seems, at least in part, to be dependent on the possible underlying causes of skeletal muscle weakness.

Physical deconditioning. To date, skeletal muscle fibre type distribution and size have never been studied in a group of consecutive patients with sarcoidosis. Moreover, the mid thigh cross-sectional area, assessed using computed tomography, and its relationship with skeletal muscle strength have never been studied. Nevertheless, physical deconditioning may be one of the underlying causes of skeletal muscle weakness in patients with sarcoidosis. For example, fatigue most probably can reduce patients' day-to-day physical activities [7]. Consequently, reduced physical activities can induce general deconditioning, which, in turn, contributes to increased perceived fatigue and more physical inactivity. Thus, patients may end up in a negative vicious circle of deconditioning. Recently, complaints of fatigue were related to skeletal muscle weakness [7] and to a lower fat-free mass over body weight ratio in patients with sarcoidosis [5]. This may all be suggestive for a role of physical deconditioning in the development and/or maintenance of skeletal muscle weakness in patients with sarcoidosis. Moreover, significant improvements in skeletal muscle force following an exercise training programme may also be indicative for the involvement of physical deconditioning in skeletal muscle weakness in patients with sarcoidosis.

Oral corticosteroids. Oral corticosteroids have shown to improve radiological abnormalities following 6–24 months of treatment and produce a small improvement in vital capacity and diffusing capacity in patients with pulmonary sarcoidosis [23]. The effects of oral corticosteroids on skeletal muscle function have not explicitly been studied in patients with sarcoidosis. Nevertheless, oral corticosteroids may have a detrimental effect on skeletal muscle force, as seen previously in elderly subjects with chronic obstructive pulmonary disease and in adults with cystic fibrosis [19, 24].

A significant inverse relationship has been found between the mean daily dose of oral steroids and quadriceps peak torque in the patients who received oral steroids in the 6-month period preceding the tests [7]. However, skeletal muscle force did not differ between patients with or without a history of oral corticosteroid treatment [6, 7]. Moreover, normal or improved skeletal muscle function has been reported after treatment with high doses of oral corticosteroids in patients with sarcoidosis [25–27]. Therefore, the effects of oral corticosteroid treatment on skeletal muscle function in patients with sarcoidosis remain unclear. Probably, these effects may be determined by the presence or absence of sarcoidosis in skeletal muscle tissue.

Sarcoidosis in skeletal muscles. The incidence and prevalence of sarcoidosis skeletal muscle involvement have never been studied in large observational studies in patients with sarcoidosis. Nonetheless, muscle involvement seems to be widely accepted [22]. This is most probably based on several studies that were undertaken ~50 yrs ago to study the possible clinical usefulness of random biopsies of the gastrocnemius muscle as a diagnostic aid in patients that were suspected of sarcoidosis. For example, MYERS *et al.* [28] described four patients with migratory polyarthritis resembling rheumatic fever or rheumatoid arthritis and with histological evidence compatible with sarcoidosis who did not have clinical manifestations referable to skeletal muscle involvement. Noncaseating epitheloid granulomas were demonstrated by lymph node biopsy in one case and by striated muscle biopsy in the remaining three cases [28]. In addition, PHILLIPS and PHILLIPS [29] reported four out of five positive muscle biopsies taken from the gastrocnemius muscle in patients that were also suspected of having sarcoidosis. Although it is noteworthy that the granulomas were found in routine muscle biopsies that were taken at random from the gastrocnemius muscle, it is be questionable whether the sarcoid-like lesions were a manifestation of rheumatoid arthritis. However, this does not appear to be likely. In fact, progressive skeletal muscle atrophy with the simultaneous presence of

discrete muscular alterations (*i.e.* wider separation of myofibrils, dilated sarcotubular system, pleomorphic mitochondria, myofibril flaking, and lipofuscin deposition in the subsarcolemmal region) are suggestive of rheumatoid myositis associated with rheumatoid arthritis [30]. It may, therefore, be reasonable that MYERS *et al.* [28] presented three patients with sarcoidosis who were likely to have muscle involvement.

More recently, open biopsies were taken from the quadriceps femoris muscle in nine nonsmoking outpatients with sarcoidosis to study the presence of noncaseating granulomas. Haematoxylin-eosin staining proved the presence of noncaseating granulomas in skeletal muscle tissue and in the endomysium in only three patients, without signs of myopathy, atrophy or peripheral neuropathy [16]. These findings are somewhat in contrast with the results of a retrospective study by PRAYSON [31], who did find electromyographic evidence for sensorimotor polyneuropathy and/or (generalised or necrotising) myopathy in six patients with sarcoidosis with clinical symptoms of muscle weakness involving the extremities, muscle pain, weight loss and paresthesias.

To date, only a few studies have used invasive techniques to study the presence of sarcoidosis in skeletal muscles in relatively small samples. The results show discrepancies, which may be in line with the heterogeneous presentation of sarcoidosis. If skeletal muscle involvement is present, a destruction of the muscle fibres previously occupying the position of the granulomas can be expected, together with early degenerative changes with loss of striation and displacement by the enlarging granulomas [28]. Skeletal muscle weakness seems to be of multiple origin in patients with sarcoidosis. Additional studies, including muscle biopsies, are necessary to unravel the underlying mechanisms of skeletal muscle weakness and dysfunction in patients with sarcoidosis.

Involuntarily weight loss

An increased inflammatory status has shown be related to involuntarily weight loss in patients with various chronic diseases [32–35]. Increased airway and systemic inflammation has also been reported in patients with sarcoidosis [7, 36, 37]. Its relationship with involuntarily weight loss has never been studied in patients with sarcoidosis. Nevertheless, some cases with severe weight loss in a short period have been reported. For example, a 26-yr-old African-American female patient with migratory polyarthritis reported a weight loss of 9.07 kg (20 lb) in 2 months, together with increasing weakness, feverishness, sweats and glands that became larger and more widely distributed [28]. Moreover, a 28-yr-old Caucasian male was readmitted to the hospital with anorexia and a weight loss of 7.26 kg (16 lb) [29]. Although nutritional support may only be beneficial for sarcoidosis patients with low body mass index (~25% of elderly patients with sarcoidosis [38]), it may be considered to be added to a multidisciplinary rehabilitation programme.

Exercise intolerance

Reduced exercise intolerance has been reported in patients with sarcoidosis. Indeed, low oxygen uptake and low external load have been found at the end of symptom-limited peak cycle ergometry tests in patients with sarcoidosis compared with healthy control subjects [7, 12–14, 39, 40]. Moreover, 6 min walk distance (6MWD) in patients with sarcoidosis differed ~200 m with the mean walking distance of healthy control subjects [7]. Exercise intolerance has been related to the excessive and inefficient ventilation and oxygen diffusing impairment [12, 14]. Moreover, skeletal muscle dysfunction has been related to exercise intolerance. Quadriceps muscle weakness was inversely related to reduced achieved peak external work load and to 6MWD in sarcoidosis patients who

complained of fatigue at the outpatient clinic, irrespective of age, sex, height and/or body weight [7]. In fact, 67% of the patients with sarcoidosis stopped the symptom-limited peak cycling exercise test due to leg complaints [13], which is most probably due to skeletal muscle weakness [41]. Unfortunately, skeletal muscle endurance has never been studied in patients with sarcoidosis, but may also be an underlying cause of reduced exercise capacity [42].

Reduced health status and quality of life

Reduced (disease specific) health status and reduced quality of life have been reported in patients with sarcoidosis and have been related to various clinical outcomes [6, 43–46]. For example, quadriceps muscle weakness was significantly related to six of the eight multiple item scales of the Medical Short Form-36 questionnaire (Spearman correlations coefficients -0.44– -0.70) [7]. In contrast, forced expiratory volume in one second and forced vital capacity were not related to the reductions in health status and sarcoidosis-related symptoms [47]. Therefore, it may be reasoned that improved muscle function can result in an improved health status in patients with sarcoidosis. In addition, the presence of symptoms of anxiety and depression have been related to a higher degree of interference of reduced physical health and increased emotional problems with normal social activities in patients with sarcoidosis [7]. Therefore, psychosocial counselling may also improve patients' health status.

Rehabilitation

Outpatient exercise training

The effects of exercise training in patients with chronic obstructive pulmonary disease have been studied extensively and have resulted in beneficial effects, such as clinically relevant improvements in perceived dyspnoea, perceived fatigue, exercise capacity and health status [48]. Moreover, exercise training as part of a multidisciplinary rehabilitation programme has shown to be of clinical benefit in patients with fibromyalgia [49] or chronic fatigue syndrome [50].

The effects of exercise training in patients with restrictive pulmonary disease have only been scantly studied. Recently, patients with post-tuberculosis lung disorder with a restrictive pulmonary function showed significant improvements in the 6MWD and on the Transition Dyspnoea Index score following 9-week outpatient exercise training programme [51]. These improvements were similar to those observed in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) and lasted up to 6 months after the termination of the exercise training programme [51]. The latter study corroborated former findings of Foster and Thomas [52], who were the first to compare the effects of a 4-week exercise training programme on 6MWD between patients with COPD and those with a diagnosis other than COPD (including pulmonary fibrosis, bronchiectasis, fibrothorax, scoliosis, lung resection and thoracoplasty). No peer-reviewed manuscripts have been published concerning the effects of exercise training in patients with sarcoidosis. Currently, the effects of a 12-week exercise training programme on disease-related quality of life and exercise capacity are studied in a prospective randomised controlled cross-over trial in the University Hospital Gasthuisberg, Leuven, Belgium. The exercise training programme consists of local dynamic resistance exercises for muscle groups of the upper and lower extremity and whole-body endurance type of exercises performed on a treadmill, cycle ergometer, arm ergometer and a step up, as

described previously [53]. Preliminary analyses showed significant median improvements in the total score on the Sarcoidosis Health Questionnaire (0.58 points), peak cycling load (17% of the predicted value, fig. 2) and cycling endurance time at 70% of the initial peak cycling load (1,319 s), while the control group remained stable [54]. Therefore, exercise training may have a positive effect on health status and exercise capacity in patients with clinically stable sarcoidosis. Exercise training may even be of greater value for those who are listed for lung transplantation. Indeed, patients with advanced sarcoidosis had a very low exercise tolerance (mean 6MWD ~310 m) [39]. This may result in a post-transplantation course with fewer complications and faster ambulation of the patients. Moreover, rehabilitation programmes are still indicated following lung transplantation. Indeed, normal daily activities did not affect exercise performance in lung transplant recipients >6 months after lung transplantation in patients with various disease [55]. Nonetheless, an aerobic exercise training programme improved submaximal and peak exercise performance significantly [55]. This is most probably due to the presence of exercise intolerance due to skeletal muscle dysfunction following lung transplantation [56].

Multidisciplinary rehabilitation

Exercise training will most probably be the cornerstone of a multidisciplinary rehabilitation programme. Additional nonpharmacological treatments, such as nutritional supplements, respiratory muscle training, and psychosocial counselling, will depend on the functional status of the patient at baseline screening. Nevertheless, nutritional supplements implemented in an 8-week rehabilitation programme resulted in significant increases in body weight and fat-free mass in depleted patients with COPD [57]. Unfortunately, oral corticosteroid treatment significantly impaired the response to nutritional supplementation therapy [57], and may, therefore, also be less effective in patients with sarcoidosis who receive oral corticosteroids. Inspiratory muscle weakness has shown to be partially reversible in patients with COPD [58]. Moreover, functional exercise capacity improved significantly in patients with a peak inspiratory mouth pressure of <60% of predicted values [58]. Finally, psychological counselling has shown to be beneficial to improve the physical activity level in patients diagnosed with chronic fatigue syndrome [59].

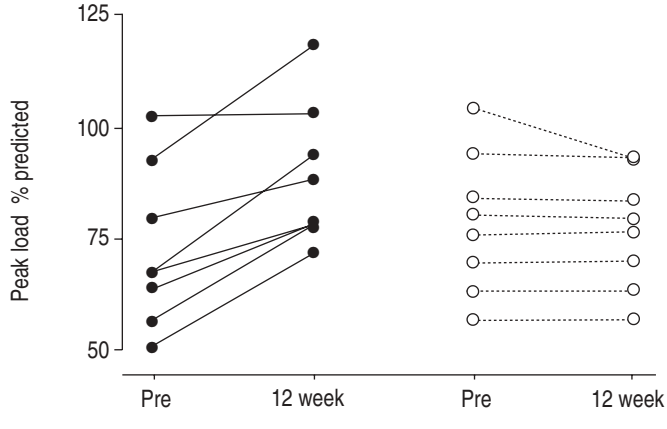

Fig. 2. – The changes over time in peak cycling load following a 12-week exercise training programme (—) or after a control period (- - -) in outpatients with sarcoidosis. Data obtained from [54].

Oxygen therapy

To date, a positive effect of home oxygen therapy on survival has not been demonstrated in patients with interstitial lung disease [60]. Nevertheless, inhaling humidified oxygen (60%) 10 min before the start of and during a constant work rate cycling endurance test at 80% of the peak load resulted in a significant increase in exercise time as compared to breathing humidified room air in 16 patients with interstitial lung disease (one patient with sarcoidosis) with a moderately severe impaired pulmonary function at rest [61]. In fact, the change in endurance time due to supplemental oxygen was inversely related to the severity of restrictive lung disease and positively to the magnitude of oxyhaemoglobin desaturation during the cycling endurance exercise in humidified room air [61]. In addition, supplemental oxygen (60%) resulted in an significant increase in peak exercise capacity in seven patients with interstitial lung disease (one patient with sarcoidosis) who all had significant arterial oxygen desaturation during an incremental cycling exercise test while breathing room air (5–16%) [62]. Supplemental oxygen during physical exercises may, therefore, be beneficial for the patients with the most manifest decrease in oxygen saturation during endurance exercises and the most striking pulmonary restriction. This topic merits further investigation.

Conclusions

Sarcoidosis is a chronic disease with many uncertainties about its pathogenesis, course, and management [63]. Exercise intolerance and reduced health status appear to be common findings in patients with sarcoidosis. However, these clinical features are not simple consequences of the changes in pulmonary function. In fact, skeletal muscle weakness and physical deconditioning have been shown to be important contributors to exercise intolerance and reduced health status in patients with sarcoidosis [6, 7]. Although the aforementioned disease-related clinical complaints have frequently been reported in patients with sarcoidosis, the effects of exercise training have not been studied in this population. Nonetheless, a clear rationale is present to study the effects of exercise training in patients with sarcoidosis. Moreover, some patients with sarcoidosis may benefit from additional therapeutic options, such as psychosocial counselling, dietary interventions and supplemental oxygen.

Summary

Daily complaints of dyspnoea and fatigue, respiratory and skeletal muscle weakness, exercise intolerance, and reduced health status and quality of life have been reported in patients with sarcoidosis, irrespective of the impaired pulmonary function. Physical inactivity may be one of the underlying causes.

Patients with sarcoidosis may benefit from an intensive exercise training programme, which has shown to improve health status, exercise capacity, skeletal muscle function and complaints of fatigue and dyspnoea in patients with other chronic diseases. Moreover, some patients with sarcoidosis may also benefit from additional therapeutic options, such as psychosocial counselling, dietary interventions and supplemental oxygen.

Preliminary results of a randomised controlled trial studying the effects of exercise training on exercise capacity and disease-specific quality of life in patients with sarcoidosis are promising. Nonetheless, this topic merits further investigations.

Keywords: Exercise capacity, exercise training, quality of life, rehabilitation, sarcoidosis, skeletal muscle.

References

1. Wirnsberger RM, de Vries J, Wouters EF, Drent M. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. *Neth J Med* 1998; 53: 53–60.
2. Lacasse Y, Brosseau L, Milne S, *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; 3: CD003793.
3. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004; 3: CD003331.
4. de Vries J, Michielsen HJ, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol* 2004; 9: 279–291.
5. Drent M, Wirnsberger RM, de Vries J, Dieijen-Visser MP, Wouters EF, Schols AM. Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999; 13: 718–722.
6. Wirnsberger RM, Drent M, Hekelaar N, *et al.* Relationship between respiratory muscle function and quality of life in sarcoidosis. *Eur Respir J* 1997; 10: 1450–1455.
7. 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: 32–38.
8. Adler RA, Funkhouser HL, Petkov VI, Berger MM. Glucocorticoid-induced osteoporosis in patients with sarcoidosis. *Am J Med Sci* 2003; 325: 1–6.
9. Casaburi R, Bhasin S, Cosentino L, *et al.* Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 870–878.
10. Wagner GJ, Rabkin JG, Rabkin R. Testosterone as a treatment for fatigue in HIV+ men. *Gen Hosp Psychiatry* 1998; 20: 209–213.
11. Baydur A, Alsalek M, Louie SG, Sharma OP. Respiratory muscle strength, lung function, and dyspnea in patients with sarcoidosis. *Chest* 2001; 120: 102–108.
12. Medinger AE, Khouri S, Rohatgi PK. Sarcoidosis: the value of exercise testing. *Chest* 2001; 120: 93–101.
13. Miller A, Brown LK, Sloane MF, Bhuptani A, Teirstein AS. Cardiorespiratory responses to incremental exercise in sarcoidosis patients with normal spirometry. *Chest* 1995; 107: 323–329.
14. Sietsema KE, Kraft M, Ginzton L, Sharma OP. Abnormal oxygen uptake responses to exercise in patients with mild pulmonary sarcoidosis. *Chest* 1992; 102: 838–845.
15. Hoitsma E, de Vries J, Santen-Hoeufft M, Faber CG, Drent M. Impact of pain in a Dutch sarcoidosis patient population. *Sarcoidosis Vasc Diffuse Lung Dis* 2003; 20: 33–39.
16. Baydur A, Pandya K, Sharma OP, Kanel GC, Carlson M. Control of ventilation, respiratory muscle strength, and granulomatous involvement of skeletal muscle in patients with sarcoidosis. *Chest* 1993; 103: 396–402.
17. Dewberry RG, Schneider BF, Cale WF, Phillips LH. Sarcoid myopathy presenting with diaphragm weakness. *Muscle Nerve* 1993; 16: 832–835.
18. Pringle CE, Dewar CL. Respiratory muscle involvement in severe sarcoid myositis. *Muscle Nerve* 1997; 20: 379–381.
19. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994; 150: 11–16.
20. Brancaleone P, Perez T, Robin S, Neviere R, Wallaert B. Clinical impact of inspiratory muscle impairment in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; 21: 219–227.
21. Man WD, Moxham J, Polkey MI. Magnetic stimulation for the measurement of respiratory and skeletal muscle function. *Eur Respir J* 2004; 24: 846–860.
22. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999; 160: 736–755.
23. Paramothayan S, Jones PW. Corticosteroid therapy in pulmonary sarcoidosis: a systematic review. *JAMA* 2002; 287: 1301–1307.

24. Barry SC, Gallagher CG. Corticosteroids and skeletal muscle function in cystic fibrosis. *J Appl Physiol* 2003; 95: 1379–1384.
25. Hearth-Holmes M, Campbell GD Jr. Muscle weakness, fatigue, and joint pain in a 52-year-old woman. *Chest* 1995; 108: 563–564.
26. Jamal MM, Cilursu AM, Hoffman EL. Sarcoidosis presenting as acute myositis. Report and review of the literature. *J Rheumatol* 1988; 15: 1868–1871.
27. Mozaffar T, Lopate G, Pestronk A. Clinical correlates of granulomas in muscle. *J Neurol* 1998; 245: 519–524.
28. Myers GB, Gottlieb AM, Mattman PE, Eckley GM, Chason JL. Joint and skeletal muscle manifestation in sarcoidosis. *Am J Med* 1952; 12: 161–169.
29. Phillips RW, Phillips AM. The diagnosis of Boeck's sarcoid by skeletal muscle biopsy. *Arch Intern Med* 1956; 98: 732–736.
30. de Palma L, Chillemi C, Albanelli S, Rapali S, Bertoni-Freddari C. Muscle involvement in rheumatoid arthritis: an ultrastructural study. *Ultrastruct Pathol* 2000; 24: 151–156.
31. Prayson RA. Granulomatous myositis. Clinicopathologic study of 12 cases. *Am J Clin Pathol* 1999; 112: 63–68.
32. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 150: 1453–1455.
33. Libera LD, Vescovo G. Muscle wastage in chronic heart failure, between apoptosis, catabolism and altered anabolism: a chimaeric view of inflammation? *Curr Opin Clin Nutr Metab Care* 2004; 7: 435–441.
34. Nelson KA, Walsh D. The cancer anorexia-cachexia syndrome: a survey of the Prognostic Inflammatory and Nutritional Index (PINI) in advanced disease. *J Pain Symptom Manage* 2002; 24: 424–428.
35. Wang AY, Sea MM, Tang N, *et al.* Resting energy expenditure and subsequent mortality risk in peritoneal dialysis patients. *J Am Soc Nephrol* 2004; 15: 3134–3143.
36. Ziegenhagen MW, Schrum S, Zissel G, Zipfel PF, Schlaak M, Muller-Quernheim J. Increased expression of proinflammatory chemokines in bronchoalveolar lavage cells of patients with progressing idiopathic pulmonary fibrosis and sarcoidosis. *J Investig Med* 1998; 46: 223–231.
37. Ziegenhagen MW, Muller-Quernheim J. The cytokine network in sarcoidosis and its clinical relevance. *J Intern Med* 2003; 253: 18–30.
38. Chevalet P, Clement R, Rodat O, Moreau A, Brisseau JM, Clarke JP. Sarcoidosis diagnosed in elderly subjects: retrospective study of 30 cases. *Chest* 2004; 126: 1423–1430.
39. Arcasoy SM, Christie JD, Pochettino A, *et al.* Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. *Chest* 2001; 120: 873–880.
40. Delobbe A, Perrault H, Maitre J, Robin S, *et al.* Impaired exercise response in sarcoid patients with normal pulmonary function. *Sarcoidosis Vasc Diffuse Lung Dis* 2002; 19: 148–153.
41. Jones NL, Killian KJ. Exercise limitation in health and disease. *N Engl J Med* 2000; 343: 632–641.
42. Van't Hul A, Harlaar J, Gosselink R, Hollander P, Postmus P, Kwakkel G. Quadriceps muscle endurance in patients with chronic obstructive pulmonary disease. *Muscle Nerve* 2004; 29: 267–274.
43. Chang B, Steimel J, Moller DR, *et al.* Depression in sarcoidosis. *Am J Respir Crit Care Med* 2001; 163: 329–334.
44. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. *Chest* 1999; 116: 1175–1182.
45. Drent M, Wirnsberger RM, Breteler MH, Kock LM, de Vries J, Wouters EF. Quality of life and depressive symptoms in patients suffering from sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998; 15: 59–66.
46. Wirnsberger RM, de Vries J, Breteler MH, Van Heck GL, Wouters EF, Drent M. Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998; 92: 750–756.

47. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. Health-related quality of life of persons with sarcoidosis. *Chest* 2004; 125: 997–1004.
48. Spruit MA, Troosters T, Trappenburg JC, Decramer M, Gosselink R. Exercise training during rehabilitation of patients with COPD: a current perspective. *Patient Educ Couns* 2004; 52: 243–248.
49. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004; 292: 2388–2395.
50. Viner R, Gregorowski A, Wine C, *et al.* Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). *Arch Dis Child* 2004; 89: 615–619.
51. Ando M, Mori A, Esaki H, *et al.* The effect of pulmonary rehabilitation in patients with post-tuberculosis lung disorder. *Chest* 2003; 123: 1988–1995.
52. Foster S, Thomas HM III. Pulmonary rehabilitation in lung disease other than chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990; 141: 601–604.
53. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance *versus* endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* 2002; 19: 1072–1078.
54. Spruit MA, Thomeer MJ, Gosselink R, Derom E, Demedts MG, Decramer M. EXercise TRAining in Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; (Abstract In press).
55. Stiebellehner L, Quittan M, End A, *et al.* Aerobic endurance training program improves exercise performance in lung transplant recipients. *Chest* 1998; 113: 906–912.
56. Evans AB, Al Himyary AJ, Hrovat MI, *et al.* Abnormal skeletal muscle oxidative capacity after lung transplantation by 31P-MRS. *Am J Respir Crit Care Med* 1997; 155: 615–621.
57. Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional aupplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 2003; 19: 120–127.
58. Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J* 2002; 20: 570–576.
59. Powell P, Bentall RP, Nye FJ, Edwards RH. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ* 2001; 322: 387–390.
60. Crockett AJ, Cranston JM, Antic N. Domiciliary oxygen for interstitial lung disease. *Cochrane Database Syst Rev* 2001; 3: CD002883.
61. Bye PT, Anderson SD, Woolcock AJ, Young IH, Alison JA. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. *Am Rev Respir Dis* 1982; 126: 1005–1012.
62. Harris-Eze AO, Sridhar G, Clemens RE, Gallagher CG, Marciniuk DD. Oxygen improves maximal exercise performance in interstitial lung disease. *Am J Respir Crit Care Med* 1994; 150: 1616–1622.
63. Martin WJ 2nd, Iannuzzi MC, Gail DB, Peavy HH. Future directions in sarcoidosis research. Summary of an NHLBI Working Group. *Am J Respir Crit Care Med* 2004; 170: 567–571.