Chapter 4

Predictors of fatigue in sarcoidosis: the value of exercise testing

B Strookappe, J De Vries, M Elfferich, P Kuijpers, T Knevel, M Drent

Respir Med 2016;116:49-54

Abstract

Background

Sarcoidosis patients often are troubled by dyspnea, exercise limitation, and fatigue. Many patients (up to 50 – 81%) suffer from sarcoidosis-associated fatigue. The etiology of fatigue in sarcoidosis is still unclear.

Objective

The aim of this study was to assess the relationship between fatigue and both exercise capacity and clinical characteristics in sarcoidosis patients. Additionally, we studied the predictive value of exercise test results and other relevant clinical characteristics for the independent variable of fatigue.

Methods

From November 2012 to September 2014, 201 sarcoidosis outpatients were referred to the Dutch ILD care expertise team, 146 of whom were included in this retrospective cohort study. All patients completed the Fatigue Assessment Scale (FAS). Exercise capacity was assessed by the 6-min walking distance (6MWD) and steep ramp test (SRT) result. Clinical data were gathered from the medical records.

Results

Exercise capacity only showed a weak correlation with fatigue (r=0.25, p=0.002 for 6MWD % of predicted; r=0.24, p=0.003 for SRT). Fatigue was not correlated with the demographic variables of age, body mass index, or time since diagnosis. Inflammatory markers, lung function tests, and hand grip strength showed no significant correlations with fatigue. Backward multiple regression analysis showed that only female sex (t=-2,614, p=0.01) and 6MWD % of predicted (t=-2.773, p=0.006) were independent predictors of fatigue. However, the r^2 indicated that these two variables together explained only 11% of the FAS score.

Conclusions

These results show that exercise capacity partly predicts patients' fatigue scores. Fatigue was not explained by lung function test results, inflammatory markers, or other clinical parameters.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by the formation of epithelioid cell granuloma without caseation. Patients often exhibit exertional dyspnea, fatigue, muscle weakness, and reduced exercise tolerance, influencing quality of life (QoL).[1-4]

Pulmonary involvement is frequent (90%). Pulmonary function tests (at rest) and imaging methods are the most commonly used examinations and diagnostic tests in the follow-up and evaluation of the therapeutic response.[5]

Several authors described the discrepancy between reported symptoms and pulmonary function test abnormalities.[6,7] Marcellis et al. found that the diffusing capacity for carbon monoxide (DLCO) at rest is an inadequate indicator of pulmonary gas exchange abnormalities during exercise.[8] Cardiopulmonary exercise testing (CPET), in order to define exercise capacity and aerobic performance, appeared to offer added value in detecting impaired gas exchange during exercise.[8]

Many patients suffer from sarcoidosis-associated fatigue, which is reported by up to 50–81% of the sarcoidosis patients [1,9]. The multifactorial etiology of fatigue in sarcoidosis is still unclear. Possible related factors are general inflammation, sleeping disorders, depression, and small-fiber neuropathy.[2] Fatigue does not correlate with pulmonary function test results, but it may be explained by peripheral muscle weakness and exercise intolerance.[2-4,10,11]

In turn, both may be explained by multiple factors, such as sarcoidosis located in the skeletal muscle, decreased pulmonary functions, physical deconditioning, and corticosteroid-induced myopathy.[2,12,13]

Cardiopulmonary exercise testing, submaximal exercise testing, and skeletal muscle function tests are therefore potentially important modalities in the follow-up and evaluation of fatigue in sarcoidosis patients.

In clinical practice, several tests are used to evaluate exercise capacity, e.g. the steep ramp test (SRT) and 6-min walk test (6MWT). The SRT is a highly reliable, accessible, and feasible maximal effort cycle ergometer exercise test for patients with pulmonary disease, and exercise responses (including oxygen consumption, minute ventilation, and oxygen saturation) are highly comparable between CPET and SRT in pulmonary patients.[14]

The 6MWT assesses the submaximal level of functional capacity, and since most activities of daily living are performed at submaximal levels of exertion, the 6-min walking distance (6MWD) may more accurately reflect the exercise level for daily physical activity.[15] Despite the fact that these tests are very different in nature and assess different aspects of the general construct of exercise capacity, exercise responses show similarities in patients with interstitial lung disease (ILD). A study by Blanco et al. found similar peak oxygen uptake values with both 6MWT and CPET in patients with ILD.[16] Strong correlations between maximal distance walked on 6MWT and maximal oxygen uptake in CPET have been reported for COPD patients.[17]

Discrepancies are often seen between test conclusions for patients performing submaximal exercise tests. A fair number of patients present with 6MWT outcomes <80% of predicted and yet achieve normal values on the SRT, and vice versa, suggesting that although both tests reflect exercise capacity, they represent different elements/components and are complementary. For this reason it can be useful to use both maximal and submaximal exercise testing in determining the construct of exercise capacity in patients with ILD.

Since the multifactorial etiology of fatigue in sarcoidosis remains unclear, the aim of this study was to assess the relationship between fatigue and both exercise capacity and clinical characteristics. More specifically, we studied the predictive value of exercise testing (including SRT and 6MWT) and other characteristics (lung function tests, body composition, radiographic stages, inflammatory markers) for the independent variable of fatigue.

Materials and methods

Study design and subjects

In this retrospective observational study, muscle strength and exercise capacity assessments were routinely performed as part of the baseline evaluation of out-patients with sarcoidosis referred to the ild care expertise team. Assessment was performed by the Department of Physical Therapy of the Gelderse Vallei Hospital, Ede, Netherlands.

Of the 201 patients evaluated between November 2012 and September 2014, 147 underwent the standard baseline evaluation, while 54 did not, for various reasons (no reason given, no combined appointment possible plus problems of traveling distance, etc.; see Figure 4.1, study flow chart). One patient did not complete the baseline physical evaluation due to inability to cycle because of pre-existent knee complaints. Finally, 146 patients were included in this retrospective observational study. None of the patients used supplemental oxygen during any of the tests.

The diagnosis of sarcoidosis was established, in accordance with accepted guidelines, by the multidisciplinary ild care expertise team.[18] Clinical data were obtained from the medical records.

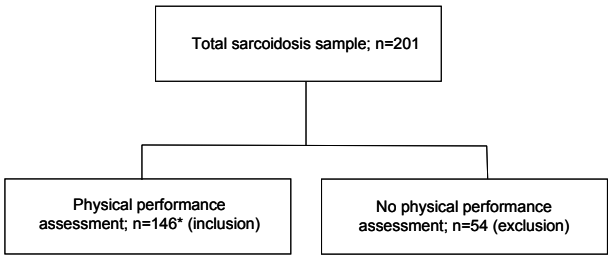

Figure 4.1 Flowchart of the study. During the study period, data of 201 outpatients suffering from sarcoidosis were collected. At baseline, the majority of these patients (n=146; * one excluded due to incomplete physical performance assessment) completed a physical assessment and surveys at the Department of Physical Therapy.

Measures

Body composition

Height (in cm), weight (in kg), and body mass index (BMI) were measured and calculated as reported previously.[19]

Lung function tests

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Values were expressed as percentage of the predicted value (i.e., FVC %, FEV_1 %, and DLCO %, respectively).

Exercise capacity

Maximal oxygen uptake was determined during a cardiopulmonary exercise test using the Steep Ramp Test (SRT) protocol on a cycle ergometer.[20] After a two-minute unloaded warm-up, the intensity was increased by 25 W every 10 seconds, with the subject pedaling at a rate of 70-80 rpm. The test was terminated when the subject indicated they could no longer continue or if the revolutions per minute fell below 60. Intermittent standardized encouragement was given to the subject throughout the test. Outcome of the SRT was used to determine estimated VO_2max value according to DeBacker and coworkers.[21] Reference values determined by Shvartz et al. were used to classify the values obtained. This classification contains the following categories: ‘excellent’, ‘very good’, ‘good’, ‘average’, ‘fair’, ‘poor’, and ‘very poor’. Maximal oxygen uptake was defined as reduced when values were classified as ‘very poor’ or ‘poor’ in the Shvartz classification.[22]

The six-minute walk test (6MWT) was administered according to the American Thoracic Society Guidelines.[15] The 6MWT is a submaximal exercise test determining the level of functional capacity. The physiologic demand in a walking test appears to be different from that in cycle ergometer tests and may be a better indicator of functioning in normal daily activities.[15,23] Predicted 6MWD values were calculated using the equation proposed by Gibson and colleagues.[24] Physical test results (6MWD) below 80% of the predicted value were assumed to indicate physical impairment.[25]

Muscle strength

The maximal isometric grip strength of the dominant hand (HGS) was measured with the Jamar dynamometer (Fabrication Enterprises Inc., Irvington, NY, USA) and expressed in kilograms (kg).[26] Percentage of predicted was calculated using normative data established by Mathiowetz and colleagues.[27] Biceps brachii strength (elbow flexor muscle strength, EFMS) was assessed during elbow flexion with the microFET (Biometrics, Almere, The Netherlands), an electronic hand-held dynamometer. The 'break' method was used to measure the peak force of the dominant arm in Newton (N). The highest value of at least two measurements was recorded.[28]

Quadriceps performance was assessed by the Chair Rise Time (CRT), which measures the time taken to rise from a chair 10 times with arms folded across the chest.[29]

Questionnaires

Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS). Each item uses a 5-point rating scale, so the total score range is 10 to 50. Scores below 22 indicate no fatigue; scores of 22-34 indicate mild-moderate fatigue; and scores of 35 or more indicate severe fatigue. The FAS has acceptable psychometric properties in sarcoidosis.[30] The minimal clinically important difference in sarcoidosis is 4 points or a 10% change.[31]

Statistical analysis

Demographic and clinical data are expressed as mean ± SD and, where appropriate, in absolute numbers or percentages. The normal distribution of the variables was evaluated with the Kolmogorov-Smirnov analysis.

Patients were subdivided into four groups according to their performance on the exercise tests (6WMT and SRT): group I (6MWD ≥80% of predicted and SRT ≥ fair), group II (6MWD <80% of predicted and SRT ≥ fair), group III (6MWD ≥80% of predicted and SRT 'very poor' / 'poor') and group IV (6MWD < 80% of predicted and SRT 'very poor' / 'poor').

Statistically significant differences between these groups with regard to demographic, clinical, fatigue, and physical characteristics were investigated by

analyzing continuous data with one-way ANOVA and examining nominal data using χ^2 tests.

Bivariate associations between fatigue and continuous demographic and physical characteristics were calculated using Pearson's correlations, while Spearman's rho was used for ordinal variables.

Variables with significant bivariate association with FAS were included as predictors in the multiple regression analysis. A backward multiple regression analysis was used to develop a model to predict fatigue. A $p<0.05$ was considered statistically significant. Analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA)

Results

Patient characteristics

The study included 146 sarcoidosis patients (mean age 47.1±11.2 years). The demographic and clinical data, subdivided into the four subgroups according to exercise capacity, are displayed in Table 4.1. The prevalence of reduced exercise capacity was high, with 75% of the patients showing a reduced 6MWD (12%), a reduced SRT VO2max (13%), or both (49%).

In our sarcoidosis patient sample, 62% of the patients had their VO_2 classified as 'very poor' to 'poor', 19% as 'fair' and 12% as 'average'. The proportion classified as 'good', 'very good' or 'excellent' was 7%. Patients with a reduced exercise capacity on both SRT and 6MWT had reduced lung function (FVC) compared with patients with normal exercise capacity. BMI differed between groups I and II, I and IV, and II and IV.

Physical performance

Muscle strength (expressed as HGS, EFMS, and CRT) was lower in patients with reduced exercise capacity (both SRT and 6MWD) compared with patients with normal exercise capacity (see Table 4.1). Exercise capacity showed low to moderate correlations with muscle strength. Correlation of 6MWD with lower limb muscle strength (CRT) was higher (r=0.48, $p<0.001$) compared to upper limb strength (r=0.27, $p=0.003$). Correlation between exercise capacity determined with SRT and lower limb muscle strength (CRT) was also higher (r=0.56, $p<0.001$) compared to upper limb strength (r=0.40, $p<0.001$).

Table 4.1 Demographic and clinical characteristics of the sarcoidosis sample (n=146) studied, subdivided according to performance on exercise test (Steep Ramp Test and 6 minute walk test)

	Group I ++	Group II +-	Group III -+	Group IV --	Group V (exclusion)	Total sample
Demographics						
Subjects (n)	37	18	19	72	54	146
women, %	48.6	22.2	47.4	36.1	42.6	39.0
age, yrs	47.7±9.8	43.1±9.1	47.4±13.8	47.4±11.6	48.9±11.3	47.1±11.2
time since diagnosis, yrs	6.0±6.5	3.6±4.7	7.7±9.5	5.9±6.9	4.7±6.5	5.9±7.0
BMI, kg/m^{2} [a,c,e]	24.3±2.7	27.8±4.8	24.4±4.6	28.8±4.5	27.0±5.8	27.0±4.6
Treatment						
no treatment, %	43.2	24.2	36.8	30.6	31.5	32.3
glucocorticoids, %	32.4	38.9	26.3	40.3	42.6	38.3
other, %	14.4	36.9	36.3	29.1	25.9	29.4
Lung function tests						
DLCO, % pred.	83.6±15.0	78.9±17.0	80.3±21.9	76.9±18.6	76.8±17.4	79.3±18.0
FEV1, % pred.	91.7±18.8	89.7±13.7	92.2±19.1	83.8±21.1	91.5±19.5	87.6±19.7
FVC, % pred.[c]	103.6±16.1	94.9±15.2	94.8±18.6	90.0±19.3	98.3±17.4	94.7±18.7
Chest radiographs stages						
0/I/II/III/IV, n	3/7/23/1/2	0/5/8/3/2	3/6/7/0/3	7/18/29/4/14	6/18/24/4/2	13/36/67/8/21
Inflammatory markers						
CRP (mg/L)	6.0±12.4	3.7 ±2.4	2.7±1.6	5.8±7.1	11.6±9.4	5.3±8.1
sIL-2R (U/ml)	4754±1775	6048±3781	3522±991	6413±9279	5894±3688	5597±6821
Fatigue measure						
FAS[c]	26.5±8.5	29.4±9.4	30.5±10.6	32.2.2±8.2	29.0±7.8	30.2±9.0
FAS physical[c]	14.8±4.9	16.0±5.2	17.2±5.5	17.9±4.3	16.4±4.3	16.7±4.9
FAS mental[c]	11.7±4.7	13.4±4.4	13.0±5.4	14.5±4.6	13.0±4.2	13.5±4.7
Physical performance						
6MWD, m[b,c,d,e]	632±68	624±46	492±81	477±82	na	536±104
6MWD, % pred.[b,c,d,e]	91.5±7.4	86.3±3.3	71.3±9.8	67.9±10.0	na	76.6±13.6
SRT (VO2max ml.kg.min)[a,c,f]	32.8±5.3	26.3±3.2	29.8±4.5	23.0±4.9	na	26.8±6.3
HGS, % pred.	96.8±17.4	96.7±14.2	81.0±30.6	89.7±23.5	na	91.1±22.7
EFMS, % pred.[c,f]	107.6±20.6	103.2±16.4	109.7±15.1	93.2±20.4	na	100.5±20.4
CRT, female (s) [c]	21.0±3.9	24.3±7.9	23.7±5.3	27.0±7.5	na	24.4±6.6
CRT, male (s) [c]	16.3±5.1	19.9±4.3	22.8±5.9	22.7±6.6	na	21.0±6.4

Data are expressed as mean ± SD, absolute numbers or percentages. BMI: body mass index; DLCO: diffusing capacity of the lung for carbon monoxide; % pred: percentage of predicted value; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; CRP: C-reactive protein; sIL-2R: soluble interleukin-2 receptor; FAS: Fatigue Assessment Scale; 6MWD: 6 min walking distance; SRT: Steep Ramp Test; HGS: maximal isometric grip strength of dominant hand; EFMS: elbow flexor muscle strength; CRT: Chair Rise Time. ++ both 6MWD and SRT normal, +- normal 6MWD, SRT reduced, -+ reduced 6MWD, SRT normal, -- reduced 6MWD, reduced SRT. P<0.05: a ++ vs +-; b ++ vs -+; c ++ vs --; d +- vs -+; e +- vs --; f -+ vs --

Relationship between fatigue and clinical parameters

The fatigue score was not correlated with the demographic variables of age, BMI, and time since diagnosis. Clinical data including inflammatory markers, lung function tests, and hand grip strength (HGS) did not show significant correlations with fatigue either.

The FAS showed a weak bivariate correlation with 6MWD (both in absolute values and percentage of predicted), SRT (both Wmax and VO_2max), EFMS % of predicted, and CRT (see Table 4.2). Women presented with significantly higher FAS scores than men (33.1±7.5 vs 28.3±9.4, p=0.002). The proportion of fatigued patients (FAS≥22) was 93% in women and 67% in men in the total population. Correlations between 6MWD and 6MWD % of predicted and SRT Rmax and SRT VO_2max were >0.80, so the variables 6MWD % of predicted and SRT VO_2max were used in the multiple regression analysis. Age, weight, and sex are taken into account in these variables.

Table 4.2 Correlations with the fatigue assessment scale (FAS).

Variables	Correlations	P-value
Sex [b]	-0.24	p=0.004
6MWD, % pred.[a]	-0.25	p=0.002
6MWD, meters [a]	-0.27	p=0.001
SRT VO_2max (ml.kg.min)[a]	-0.24	p=0.003
SRT Rmax [a]	-0.27	p=0.001
EFMS, % pred.[a]	-0.23	p=0.011
CRT[a]	-0.21	p=0.022

[a] Pearson's correlation coefficient; [b] Spearman's rho. 6MWD: 6 min walking distance; SRT: Steep Ramp Test; EFMS: elbow flexor muscle strength; CRT: Chair Rise Time.

Multiple regression analysis showed that female sex (t=-2,614, p=0.01) and 6MWD % of predicted (t=-2.773, p=0.006) were significant independent predictors of FAS. However, the resulting r^2 indicated that these two variables explained only 11% of the FAS score.

These two variables were also found to be independent predictors of the physical component of the FAS. Only the SRT VO2 max appeared to be an independent predictor of the mental component of the FAS (see Table 3).

Table 4.3 Multiple regression analysis: relationship between the Fatigue Assessment Scale (FAS, FAS physical component and FAS mental component) and clinical variables.

Outcome variable	Independent variables	Unstandardized coefficient		Standardized coefficients	P-value
		B	Std error	Beta	
FAS total	sex	-4.015	1.536	-0.223	p=0.01
	6MWD, % pred.	-0.152	0.055	-0.246	p=0.006
FAS physical	sex	-2.370	0.813	-0.245	p=0.004
	6MWD, % pred.	-0.089	0.029	-0.258	p=0.003
FAS mental	SRT, VO_2max	-0.182	0.063	-0.251	p=0.005

6MWD: 6 min walking distance; SRT: Steep Ramp Test.

Discussion

The aim of this study was to assess the relationship between fatigue and both exercise capacity and clinical characteristics in patients with sarcoidosis. In our cohort, the prevalence of fatigue (FAS≥22) was high (77%), as was reduced exercise capacity (75%). Exercise capacity only showed a weak correlation with fatigue. In line with other studies, we found that the level of fatigue was not explained by lung function test results, nor inflammatory markers or other clinical parameters.[1,11] Female sex and 6MWD% of predicted only predicted 11% of the FAS score.

Women presented with significantly higher FAS scores than men, and more women were fatigued. It has been shown that fatigue is more likely to be present and more severe in patients with extrapulmonary symptoms[32] and female sarcoidosis patients report more frequent extrapulmonary complaints and musculoskeletal involvement.[33] This may at least partly explain the differences between male and female patients. There were no differences between the men and women in terms of lung function test results, inflammatory markers, BMI, or chest radiography stages.

Our results support the view that fatigue in sarcoidosis is an entity which is affected by many different variables, since exercise capacity explains only a small proportion of the variance of the reported fatigue. Spruit et al. suggested that fatigue may be explained by muscle weakness and exercise intolerance, due to sarcoidosis located in the skeletal muscle, decreased pulmonary functions, and the negative vicious circle of deconditioning and corticosteroid-induced myopathy.[12] In a retrospective study, Cremers et al. found muscle involvement in only 12% of the PET (positron emission tomography) positive cases (n=118).[34] This number is probably underestimated, as it only gives information about PET-positive cases. In line with others, our present study found that there is no relationship between fatigue and pulmonary functions.[35] Although it is highly likely that a negative vicious circle of deconditioning also influences the relation, no studies investigating this have been done.

Fleischer et al.[36] found associations between medication (prednisolone, methotrexate, and azathioprine) and fatigue, but patients who never used corticosteroids also suffer from fatigue.[35,37]

Few studies on sarcoidosis have reported that perceived fatigue can be decreased by following a physical training program to improve exercise capacity and muscle functions (strength and endurance).[3,38-40] Some patients may present with impaired exercise capacity, impaired muscle function or both, and a tailored training intervention may then result in a better outcome. Hence, the use of exercise testing and muscle function analysis is important when prescribing, monitoring, and evaluating a physical training program.

The importance of exercise testing in sarcoidosis was highlighted by Marcellis et al..[8] The 6MWT has also proven its value in the evaluation of exercise capacity in sarcoidosis.[41] A recent study found that CPET appeared to offer added value in detecting impaired gas exchange during exercise.[8] Moreover, Lopes et al. found that

CPET can be helpful in predicting decline in pulmonary functions.[42] However, CPET requires extensive equipment, is time-consuming and not available in every clinical setting.[8] The Steep Ramp Test (SRT) is a cardiopulmonary maximal effort test which assesses maximal oxygen uptake. It is a highly reliable, accessible, and feasible instrument for patients with pulmonary disease.[14,43]

In our study we found discrepancies between test conclusions in 25% of the cases of patients performing (sub)maximal exercise tests (6MWT vs SRT). These outcomes suggest that these two tests represent different elements of exercise capacity, and are complementary. Mainguy and colleagues state that despite a similar physiological demand in terms of VO_2peak, the modality of the exercise test (cycling vs walking) was mainly responsible for the differences in respiratory exchange ratio, locus of symptom limitation, and leg muscle fatigability.[44]

When CPET is not available, the SRT can be a useful alternative, in view of its similar exercise responses.[14] The SRT can be regularly repeated during the training program, providing the information needed to adjust the training dosage or evaluate the exercise response.[21] Additionally, the SRT accurately reflects leg muscle capabilities during exercise, whereas CPET may underestimate muscle power due to the attainment of ventilatory limitations.[14,43] In our present study, correlations between SRT and leg muscle power (CRT) were moderate (data not shown).

Peripheral/skeletal muscle strength is often reduced in sarcoidosis. Patients with impaired muscle strength are more likely to present with lower QoL, lung function test results, and 6MWD.[1,12] Assessing skeletal muscle function in sarcoidosis is recommended for patients with impaired exercise capacity. It is therefore important to determine the potential influence of muscle function on exercise capacity in each individual patient with impaired exercise capacity. Upper limb strength is often measured as hand grip strength or elbow flexor muscle strength. One option to determine lower limb muscle strength is hand-held dynamometry. However, despite the reduced muscle strength of patients with sarcoidosis, the value of hand-held dynamometry in assessing lower limb muscle strength often appears to be limited, as the patient's strength, especially that of younger male patients, exceeds that of the assessor.[45,46] The CRT therefore appears to be a valuable alternative. There are strong correlations between several variations of sit-to-stand tests (including CRT) and lower limb muscle strength in pulmonary restricted patients, as shown by our results in this study.[47]

This study has several limitations. Although the choice of tests was carefully considered,[23,41] other tests might have been useful as well. The voluntary nature of the submaximal exercise tests used in this study may influence the test results, as motivation and will power are important factors, so nonvolitional testing would probably yield more valid results. But in our opinion, as was also stated by Marcellis et al., sarcoidosis patients present with great motivation to participate.[1] The tests used in our study are generally accepted and have been used in various patient populations, including sarcoidosis patients.[12,41] Our study population included 146 analyzed patients.

Groups were created according to the patients' performance on the exercise tests (6MWD and SRT), resulting in groups with rather small numbers, which potentially limits the generalization of the results of our study.

Conclusion

While it is well known that sarcoidosis-related fatigue is multi-factorial in nature, our study failed to discover any meaningful associations based on the available data for this patient sample. While very small relationships were observed between fatigue and exercise capacity, female sex, and a 6-minute walk test, caution should be used when interpreting these findings given the different limitations described above. Further research to clarify the phenomenon of fatigue in sarcoidosis is important, in order to enhance both medical and paramedical fatigue reduction strategies.

References

1. Marcellis RG, Lenssen AF, Elfferich MD, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J 2011;38:628-634.
2. Drent M, Strookappe B, Hoitsma E, De Vries J. Consequences of Sarcoidosis. Clin Chest Med 2015;36:727-737.
3. Karadalli MN, Bosnak-Guclu M, Camcioglu B, Kokturk N, Turktas H. Effects of Inspiratory Muscle Training in Subjects With Sarcoidosis: A Randomized Controlled Clinical Trial. Respir Care 2016;61: 483-494.
4. Panagiotou M, Polychronopoulos V, Strange C. Respiratory and lower limb muscle function in interstitial lung disease. Chron Respir Dis 2016:doi 10.1177/1479972315626014.
5. Gafa G, Sverzellati N, Bonati E, et al. Follow-up in pulmonary sarcoidosis: comparison between HRCT and pulmonary function tests. Radiol Med 2012;117:968-978.
6. Delobbe A, Perrault H, Maitre J, et al. Impaired exercise response in sarcoid patients with normal pulmonary function. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:148-153.
7. Kollert F, Geck B, Suchy R, et al. The impact of gas exchange measurement during exercise in pulmonary sarcoidosis. Respir Med 2011;105:122-129.
8. Marcellis RG, Lenssen AF, de Vries GJ, et al. Is there an added value of cardiopulmonary exercise testing in sarcoidosis patients? Lung 2013;191:43-52.
9. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J 2012;40:255-263.
10. Drent M, Wirnsberger RM, De Vries J, van Dieijen-Visser MP, Wouters EF, Schols AM. Association of fatigue with an acute phase response in sarcoidosis. Eur Respir J 1999;13:718-722.
11. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:127-136.
12. 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.
13. Wilsher ML. Psychological stress in sarcoidosis. Curr Opin Pulm Med 2012;18:524-527.
14. Chura RL, Marciniuk DD, Clemens R, Butcher SJ. Test-Retest Reliability and Physiological Responses Associated with the Steep Ramp Anaerobic Test in Patients with COPD. Pulm Med 2012;2012:653831.
15. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
16. Blanco I, Villaquiran C, Valera JL, et al. [Peak oxygen uptake during the six-minute walk test in diffuse interstitial lung disease and pulmonary hypertension]. Arch Bronconeumol 2010;46:122-128.
17. Chuang ML, Lin IF, Wasserman K. The body weight-walking distance product as related to lung function, anaerobic threshold and peak VO2 in COPD patients. Respir Med 2001;95:618-626.
18. 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.
19. Cremers JP, Drent M, Elfferich MD, et al. Body composition profiling in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:289-299.
20. Meyer K, Samek L, Schwaibold M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure--application to exercise training. Eur Heart J 1996;17:1040-1047.
21. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. Arch Phys Med Rehabil 2007;88:610-616.
22. Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. Aviation, space, and environmental medicine 1990;61:3-11.
23. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. Phys Ther 2000;80:782-807.
24. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. J Cardiopulm Rehabil 2001;21:87-93.
25. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. Eur Respir J 1999;14:270-274.
26. Werle S, Goldhahn J, Drerup S, Simmen BR, Sprott H, Herren DB. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. J Hand Surg Eur Vol 2009;34:76-84.

27. Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther 1986;40:705-711.
28. Bohannon RW. Make tests and break tests of elbow flexor muscle strength. Phys Ther 1988;68: 193-194.
29. Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strength. Am J Med 1985;78:77-81.
30. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest 2006;130:989-994.
31. De Kleijn WP, De Vries J, Wijnen PA, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. Respir Med 2011;105:1388-1395.
32. Gvozdenovic BS, Mihailovic-Vucinic V, Ilic-Dudvarski A, Zugic V, Judson MA. Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis. Respir Med 2008;102:1636-1642.
33. Lill H, Kliiman K, Altraja A. Factors signifying gender differences in clinical presentation of sarcoidosis among Estonian population. Clin Resp J 2016;10:282-90.
34. Cremers JP, Van Kroonenburgh MJ, Mostard RL, et al. Extent of disease activity assessed by 18F-FDG PET/CT in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis 2014;31:37-45.
35. Marcellis RG, Lenssen AF, Kleynen S, De Vries J, Drent M. Exercise capacity, muscle strength, and fatigue in sarcoidosis: a follow-up study. Lung 2013;191:247-256.
36. Fleischer M, Hinz A, Brahler E, Wirtz H, Bosse-Henck A. Factors associated with fatigue in sarcoidosis. Respir Care 2014;59:1086-1094.
37. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. Respiration 2010;80:212-219.
38. Strookappe B, Elfferich M, Swigris J, et al. Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. Sarcoidosis Vasc Diffuse Lung Dis 2015;32:43-52.
39. Strookappe B, Swigris J, De Vries J, Elfferich M, Knevel T, Drent M. Benefits of Physical Training in Sarcoidosis. Lung 2015
40. Marcellis RG, Veeke MAF, Mesters I, et al. Does physical training reduce fatigue in sarcoidosis? Sarcoidosis Vasc Diffuse Lung Dis 2015;32:53-62.
41. Baughman RP, Lower EE. Six-minute walk test in managing and monitoring sarcoidosis patients. Curr Opin Pulm Med 2007;13:439-444.
42. Lopes AJ, Menezes SL, Dias CM, Oliveira JF, Mainenti MR, Guimaraes FS. Cardiopulmonary exercise testing variables as predictors of long-term outcome in thoracic sarcoidosis. Braz J Med Biol Res 2012;45:256-263.
43. Rozenberg R, Bussmann JB, Lesaffre E, Stam HJ, Praet SF. A steep ramp test is valid for estimating maximal power and oxygen uptake during a standard ramp test in type 2 diabetes. Scand J Med Sci Sports 2015;25:595-602.
44. Mainguy V, Malenfant S, Neyron AS, et al. Alternatives to the six-minute walk test in pulmonary arterial hypertension. PloS one 2014;9:e103626.
45. Wikholm JB, Bohannon RW. Hand-held Dynamometer Measurements: Tester Strength Makes a Difference. J Orthop Sports Phys Ther 1991;13:191-198.
46. Lu TW, Hsu HC, Chang LY, Chen HL. Enhancing the examiner's resisting force improves the reliability of manual muscle strength measurements: comparison of a new device with hand-held dynamometry. J Rehabil Med 2007;39:679-684.
47. Aguilaniu B, Roth H, Gonzalez-Bermejo J, et al. A simple semipaced 3-minute chair rise test for routine exercise tolerance testing in COPD. Int J Chron Obstruct Pulmon Dis 2014;9:1009-1019.