Chapter 4

Predictors of fatigue in sarcoidosis: the value of exercise testing

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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).\textsuperscript{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.\textsuperscript{5}

Several authors described the discrepancy between reported symptoms and pulmonary function test abnormalities.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8}

Many patients suffer from sarcoidosis-associated fatigue, which is reported by up to 50–81% of the sarcoidosis patients.\textsuperscript{1,5} The multifactorial etiology of fatigue in sarcoidosis is still unclear. Possible related factors are general inflammation, sleeping disorders, depression, and small-fiber neuropathy.\textsuperscript{2} Fatigue does not correlate with pulmonary function test results, but it may be explained by peripheral muscle weakness and exercise intolerance.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} Strong correlations between maximal distance walked on 6MWT and maximal oxygen uptake in CPET have been reported for COPD patients.\textsuperscript{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 outpatients 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. Clinical data were obtained from the medical records.
Predictors of fatigue in sarcoidosis

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 (FEV1) 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 %, FEV1 %, 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 VO2max 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.\textsuperscript{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.\textsuperscript{15,23} Predicted 6MWD values were calculated using the equation proposed by Gibson and colleagues.\textsuperscript{24} Physical test results (6MWD) below 80\% of the predicted value were assumed to indicate physical impairment.\textsuperscript{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).\textsuperscript{26} Percentage of predicted was calculated using normative data established by Mathiowetz and colleagues.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{30} The minimal clinically important difference in sarcoidosis is 4 points or a 10\% change.\textsuperscript{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 $\chi^2$ 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 VO2 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)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group I ++</th>
<th>Group II +</th>
<th>Group III +</th>
<th>Group IV -</th>
<th>Group V (exclusion)</th>
<th>Total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>37</td>
<td>18</td>
<td>19</td>
<td>72</td>
<td>54</td>
<td>146</td>
</tr>
<tr>
<td>women, %</td>
<td>48.6</td>
<td>22.2</td>
<td>47.4</td>
<td>36.1</td>
<td>42.6</td>
<td>39.0</td>
</tr>
<tr>
<td>age, yrs</td>
<td>47.7±9.8</td>
<td>43.1±9.1</td>
<td>47.4±13.8</td>
<td>47.4±11.6</td>
<td>48.9±11.3</td>
<td>47.1±11.2</td>
</tr>
<tr>
<td>time since diagnosis, yrs</td>
<td>6.0±6.5</td>
<td>3.6±4.7</td>
<td>7.7±9.5</td>
<td>5.9±6.9</td>
<td>4.7±6.5</td>
<td>5.9±7.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3±2.7</td>
<td>27.8±4.8</td>
<td>24.4±4.6</td>
<td>28.8±4.5</td>
<td>27.0±5.8</td>
<td>27.0±4.6</td>
</tr>
<tr>
<td>Treatment no treatment, %</td>
<td>43.2</td>
<td>24.2</td>
<td>36.8</td>
<td>30.6</td>
<td>31.5</td>
<td>32.3</td>
</tr>
<tr>
<td>glucocorticoids, %</td>
<td>32.4</td>
<td>38.9</td>
<td>26.3</td>
<td>40.3</td>
<td>42.6</td>
<td>38.3</td>
</tr>
<tr>
<td>other, %</td>
<td>14.4</td>
<td>36.9</td>
<td>36.3</td>
<td>29.1</td>
<td>25.9</td>
<td>29.4</td>
</tr>
</tbody>
</table>

**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. | 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**

**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 | 559716821 |

**Fatigue measure**
- FAS | 26.5±8.5 | 29.4±9.4 | 30.5±10.6 | 32.2±8.9 | 29.0±7.8 | 30.2±9.0 |
- FAS physical | 14.8±4.9 | 16.0±5.2 | 17.2±5.5 | 17.9±4.3 | 16.4±3.4 | 16.7±4.9 |
- FAS mental | 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 | 632±68 | 624±46 | 492±81 | 477±82 | na | 536±104 |
- 6MWD, % pred. | 91.5±7.4 | 86.3±3.3 | 71.4±9.8 | 67.9±10.0 | na | 76.6±13.6 |
- SRT (VO2max ml/kg.min) | 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. | 107.6±20.6 | 103.2±16.4 | 109.7±15.1 | 93.2±20.4 | na | 100.5±20.4 |
- CRT, female (s) | 21.0±3.9 | 24.3±7.9 | 23.7±5.3 | 27.0±7.5 | na | 24.4±6.6 |
- CRT, male (s) | 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; FEV₁: 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 VO2max), 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 VO2max were >0.80, so the variables 6MWD % of predicted and SRT VO2max 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).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlations</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-0.24</td>
<td>p=0.004</td>
</tr>
<tr>
<td>6MWD % pred</td>
<td>-0.25</td>
<td>p=0.002</td>
</tr>
<tr>
<td>6MWD meters</td>
<td>-0.27</td>
<td>p=0.001</td>
</tr>
<tr>
<td>SRT VO2max (ml.kg.min)</td>
<td>-0.24</td>
<td>p=0.003</td>
</tr>
<tr>
<td>SRT Rmax</td>
<td>-0.27</td>
<td>p=0.001</td>
</tr>
<tr>
<td>EFMS % pred</td>
<td>-0.23</td>
<td>p=0.011</td>
</tr>
<tr>
<td>CRT</td>
<td>-0.21</td>
<td>p=0.022</td>
</tr>
</tbody>
</table>

* Pearson's correlation coefficient; * 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.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Independent variables</th>
<th>Unstandardized coefficient</th>
<th>Standardized coefficients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS total</td>
<td>sex</td>
<td>-4.015</td>
<td>-0.223</td>
<td>p=0.01</td>
</tr>
<tr>
<td></td>
<td>6MWD % pred.</td>
<td>-0.152</td>
<td>-0.246</td>
<td>p=0.006</td>
</tr>
<tr>
<td>FAS physical</td>
<td>sex</td>
<td>-2.370</td>
<td>-0.245</td>
<td>p=0.004</td>
</tr>
<tr>
<td></td>
<td>6MWD % pred.</td>
<td>-0.089</td>
<td>-0.258</td>
<td>p=0.003</td>
</tr>
<tr>
<td>FAS mental</td>
<td>SRT VO2max</td>
<td>-0.182</td>
<td>-0.251</td>
<td>p=0.005</td>
</tr>
</tbody>
</table>

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. 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 and female sarcoidosis patients report more frequent extrapulmonary complaints and musculoskeletal involvement. 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. In a retrospective study, Cremers et al. found muscle involvement in only 12% of the PET (positron emission tomography) positive cases (n=118). 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. 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. found associations between medication (prednisolone, methotrexate, and azathioprine) and fatigue, but patients who never used corticosteroids also suffer from fatigue.

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). 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. The 6MWT has also proven its value in the evaluation of exercise capacity in sarcoidosis. A recent study found that CPET appeared to offer added value in detecting impaired gas exchange during exercise. Moreover, Lopes et al. found that
CPET can be helpful in predicting decline in pulmonary functions.\textsuperscript{42} However, CPET requires extensive equipment, is time-consuming and not available in every clinical setting.\textsuperscript{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.\textsuperscript{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 \( \text{VO}_2\text{peak} \), 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.\textsuperscript{44}

When CPET is not available, the SRT can be a useful alternative, in view of its similar exercise responses.\textsuperscript{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.\textsuperscript{21} Additionally, the SRT accurately reflects leg muscle capabilities during exercise, whereas CPET may underestimate muscle power due to the attainment of ventilatory limitations.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47}

This study has several limitations. Although the choice of tests was carefully considered,\textsuperscript{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.\textsuperscript{1} The tests used in our study are generally accepted and have been used in various patient populations, including sarcoidosis patients.\textsuperscript{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

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.


