Exercise capacity, muscle strength and fatigue in sarcoidosis

R.G.J. Marcellis*,#, A.F. Lenssen*, M.D.P. Elfferich*,#, J. De Vries*,#,r, S. Kassim*, K. Foerster* and M. Drent #,*

**ABSTRACT:** The aim of this case–control study was to investigate the prevalence of exercise intolerance, muscle weakness and fatigue in sarcoidosis patients. Additionally, we evaluated whether fatigue can be explained by exercise capacity, muscle strength or other clinical characteristics (lung function tests, radiographic stages, prednisone usage and inflammatory markers).

124 sarcoidosis patients (80 males) referred to the Maastricht University Medical Centre (Maastricht, the Netherlands) were included (mean age 46.6 ± 10.2 yrs). Patients performed a 6-min walk test (6MWT) and handgrip force (HGF), elbow flexor muscle strength (EFMS), quadriceps peak torque (QPT) and hamstring peak torque (HPT) tests. Maximal inspiratory pressure ($P_{I,max}$) was recorded. All patients completed the Fatigue Assessment Scale (FAS) questionnaire.

The 6MWT was reduced in 45% of the population, while HGF, EFMS, QPT and HPT muscle strength were reduced in 15, 12, 27 and 18%, respectively. $P_{I,max}$ was reduced in 43% of the population. The majority of the patients (81%) reported fatigue (FAS ≥ 22). Patients with reduced peripheral muscle strength of the upper and/or lower extremities were more fatigued and demonstrated impaired lung functions, fat-free mass, $P_{I,max}$, 6MWT and quality of life. Fatigue was neither predicted by exercise capacity, nor by muscle strength.

Besides fatigue, exercise intolerance and muscle weakness are frequent problems in sarcoidosis. We therefore recommend physical tests in the multidisciplinary management of sarcoidosis patients, even in nonfatigued patients.

**KEYWORDS:** Exercise capacity, fatigue, inspiratory muscle strength, peripheral muscle strength, sarcoidosis

Sarcoidosis is a multisystem disorder of unknown origin, which is characterised by noncaseating epithelioid cell granulomas. The clinical course of sarcoidosis is highly variable, and virtually every organ can be involved. The lungs are affected in >90% of sarcoidosis patients, but muscles are also frequently involved. Patients often present with nonspecific symptoms, such as general weakness, arthralgia, reduced exercise capacity and fatigue [1].

Despite the fact that fatigue is a common disabling problem (with a reported prevalence of 30–90%) and a clear hallmark of sarcoidosis patients that affects quality of life (QoL), it still remains underestimated and poorly understood [2]. The aetiology of fatigue in sarcoidosis is still unclear, and is most probably multifactorial. Moreover, fatigue is difficult to objectify. Possible factors related to fatigue are general inflammation, sleeping disorders, depression and small-fibre neuropathy [3]. However, fatigue does not correlate with lung function test results [2, 4]. Fatigue may be explained by peripheral muscle weakness and exercise intolerance, and both may be caused by multiple factors, such as sarcoidosis located in the skeletal muscle, decreased pulmonary function, negative vicious circle of physical deconditioning and corticosteroid-induced myopathy [5].

The influence of exercise capacity and muscle strength on fatigue has not been studied extensively in sarcoidosis, although reduced exercise capacity and general weakness are frequently reported symptoms. Patients with fatigue complaints are more likely to report problems of exercise intolerance compared with nonfatigued patients [4]. The 6-min walk test (6MWT) is widely used to assess exercise capacity [6]. Previous research found that the 6-min walking distance (6MWD) was reduced in sarcoidosis patients compared with healthy subjects [7, 8].
Impairment of inspiratory muscle strength has been suggested as an important factor reducing 6MWD [9]. Alhamad [7] and Baughman et al. [8] found that 73% and 51% of their respective sarcoidosis populations had a 6MWD of <400 m.

In a study by Miller et al. [10], 67% of the sarcoidosis patients terminated their peak exercise test because of “leg complaints”, which was considered an indication of skeletal muscle weakness. Similarly, Spruit et al. [5] reported diminished peripheral muscle strength in patients with sarcoidosis suffering from fatigue, and reduced peripheral muscle strength correlated with exercise intolerance and fatigue. In line with this, Wernzberger et al. [11] found reduced respiratory muscle strength and endurance time. However, the study populations were rather small or only included sarcoidosis patients with specific health complaints.

The primary aim of our study was to assess the prevalence of exercise intolerance, peripheral muscle weakness and fatigue in sarcoidosis patients. Additionally, the predictive value of exercise capacity, muscle strength and other clinical characteristics, including lung function test results, radiographic stages, prednisone usage and inflammatory markers, were studied.

METHODS

Subjects
Between November 2008 and September 2009, symptomatic sarcoidosis patients referred to the interstitial lung disease care team of the Dept of Respiratory Medicine at Maastricht University Medical Centre (MUMC; Maastricht, the Netherlands) were included in this study. Patients were diagnosed based on consistent clinical features and bronchoalveolar lavage fluid analysis, and/or biopsy-proven noncaseating epithelioid cell granulomas, according to the WASOG (World Association of Sarcoidosis and Other Granulomatous Disorders) guidelines [1]. Clinical data were obtained from medical records. A healthy control group matched for age and sex (one control for two patients) was recruited from hospital employees and the surrounding community. These healthy subjects did not use any medication. The data were used as reference for exercise capacity and peripheral muscle strength. Written informed consent was obtained from all subjects. This case-control study was approved by the local Medical Ethics Committee of the MUMC.

Clinical data
At inclusion, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured with a pneumotachograph (Masterlab; Jaeger, Würzburg, Germany). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab; Jaeger). Values were expressed as percentage of predicted value [12].

Chest radiographs were graded according to the radiographic staging proposed by DeRemee (0 to III), adding stage IV, for patients showing signs of pulmonary fibrosis, loss of lung volume, hilar retraction and bullae [1].

Body composition was measured by single-frequency bioelectrical impedance analysis (RJL Systems Inc., Clinton Township, MI, USA) in the supine position on the right side. Fat-free mass (FFM) was calculated from height (m²)/resistance and body weight using the Lukaski formula. In order to assess the degree of functional tissue depletion, FFM was adjusted for body size by calculating the FFM index: FFM (kg)/height (m²) [4].

The C-reactive protein (CRP) concentration was measured by a turbidimetric method on the SYNCHRON LX (Beckman Coulter Inc., Fullerton, CA, USA). The normal value for CRP is <10 mg L⁻¹. The serum levels of soluble interleukin-2 receptor (sIL-2R) were analysed using commercially available Diaclene ELISA kits (Sanquin, Amsterdam, the Netherlands). Normal values are between 240 and 3,154 pg mL⁻¹.

Muscle strength and exercise capacity
The 6MWT was used to assess exercise capacity, and was performed according to the American Thoracic Society guidelines [13].

The Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, New York, USA) was used to measure isokinetic peak torques (in Nm) of the hamstrings and quadriceps of the dominant leg, with a velocity of 180° per second, as described previously [14]. The Biodex is a reliable and valid isokinetic dynamometer [15].

The maximal isometric grip strength of the dominant hand (lbs) was measured with the Jamar dynamometer (Fabrication Enterprises Inc., Irvington, NY, USA), which is also a valid and reliable instrument [16].

Maximal isometric strength of the elbow flexors was measured with the microFET (Biometrics, Almere, the Netherlands), an electronic, hand-held dynamometer, with the subject sitting in a chair. The “break” method was used to measure the maximal peak force of the dominant arm in Newtons (N) [17]. This hand-held dynamometer is a reliable instrument [17].

Maximal inspiratory pressure (Pl,max) was assessed by measuring maximal respiratory mouth pressures using the method of Black and Hyatt [18]. Maximal inspiratory mouth pressure was measured at residual volume with a pressure transducer (model MP 45–30; Validyne Engineering Corp., Northridge, CA, USA) [4]. Data from the study by Harik-Khan et al. [19] (n=267 healthy subjects) were used as reference values.

Questionnaires
Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS), which indicates both physical and psychological fatigue. Each item has a five-point rating scale and FAS scores range from 10 to 50. FAS scores <22 indicate nonfatigued persons, scores of 22–34 indicate fatigued persons and scores of >35 indicate extremely fatigued persons [20]. The psychometric properties of the FAS are also good in sarcoidosis [20].

The World Health Organization Quality of Life assessment instrument-BREF (WHOQOL-BREF) is a generic, cross-culturally developed comprehensive measure of QoL. It consists of 24 questions within four domains (physical health, psychological health, social relationships and environment) and two questions that compose the facet of overall QoL and general health. The psychometric properties of the WHOQOL-BREF appeared to be good [21, 22].

Statistical analysis
Demographic and clinical data are expressed as mean ± SD and, if appropriate, in absolute numbers. To detect statistically
significant differences between the patient and control groups, continuous data were analysed with independent-sample unpaired t-tests and nominal data were tested using Chi-squared tests.

Physical test results below the mean results of the control group minus 2sd (95% confidence interval) were assumed to indicate exercise intolerance or muscle strength impairment. The cut-off value for $P_{\text{max}}$, FVC, FEV1 and $D_L,\text{CO}$ was <80% of the predicted value [12, 19]. Frequency distributions were used to determine the prevalence of exercise intolerance, reduced muscle strength and fatigue.

Associations between exercise capacity, muscle strength, fatigue and other clinical characteristics were calculated using Pearson’s correlations. Differences in FAS scores in relation to sex, prednisone use and radiographic stages were explored by means of t-tests and one-way ANOVA. Variables with a significant association with fatigue were used for multiple regression analysis. A backward multiple regression analysis was used to develop a model to predict fatigue. A p-value <0.05 was considered to be statistically significant.

Differences between sarcoidosis patients with (group 4: combination of patients in group 2 (reduced muscle strength of arms) and group 3 (reduced muscle strength of legs)) and without (group 1: normal muscle strength of both arms and legs) peripheral muscle strength impairment with regard to physical and clinical characteristics were examined using independent-sample t-tests. Differences in nominal data were tested using Chi-squared tests. All analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient and healthy control characteristics

During the study period, 145 sarcoidosis patients were referred to the outpatient clinic of the MUMC. 21 of the patients were not able to participate because they visited the hospital in a week when the maximum inclusion capacity of five subjects had already been reached. Thus, 124 sarcoidosis patients (mean age 46.6 ± 10.2 yrs; 80 males and 44 females) were included. Clinical data are summarised in table 1. FAS scores >21 points, indicating fatigue complaints, were reported in 101 (81%) patients, and 26% of these fatigued patients reported extreme fatigue (FAS ≥35). The mean body mass index (BMI) was 28.0 ± 4.7 kg·m⁻², which indicated some excess weight (BMI between 25–30 kg·m⁻² indicates overweight). The pulmonary function tests showed that FEV1 and $D_L,\text{CO}$, as a percentage of predicted values, were slightly reduced in this population. The clinical data of the healthy control group are also presented in table 1. Sarcoidosis patients were significantly more fatigued compared with the healthy controls (p<0.001).

Exercise capacity

Sarcoidosis patients demonstrated a significantly shorter 6MWD compared with healthy controls (table 2). The sarcoidosis population showed a mean reduction in exercise capacity of 20% (table 2), >45% of the sarcoidosis patients demonstrated a reduction in exercise capacity.

Exercise capacity was reduced in 49% of the fatigued and in 30% of the nonfatigued patients (p=0.116). Patients with peripheral muscle strength impairment demonstrated a reduced 6MWD compared with patients without reduced peripheral muscle strength (p<0.001) (table 3).

Muscle strength

Peripheral muscle strength, i.e. elbow flexor muscle strength, and quadriceps and hamstrings peak torque, was significantly lower in the sarcoidosis patients compared to the control subjects (table 2). No differences were found in handgrip force between both groups.

Handgrip force, elbow flexor muscle strength, quadriceps peak torque, hamstrings peak torque and $P_{\text{max}}$ were reduced in 15, 12, 27, 18 and 43% of the population, respectively (table 2).

A substantial proportion of the fatigued and nonfatigued patients showed a reduction in handgrip force (18% and 4%, respectively; p=0.102), elbow flexor muscle strength (12% and
Peripheral muscle strength nor reduced peripheral muscle strength compared to patients 6MWD, were found to be impaired in the subgroup with did not differ regarding sex (t 5 0.507 (df regression 4, df residual 119), p 5 0.5). The overall QoL and the QoL domain physical health, as well as the lung function test results, FFM, and muscle force parameters in male patients but not in female patients (table 4). In the female patients only, BMI (r 5 0.314) or radiographic stages (F-score 5 0.114). In multiple regression analyses, only hamstrings peak torque was a significant predictor of fatigue in male patients, predicting 14.3% of the FAS score (p 5 0.001; β = 0.114).

**DISCUSSION**

The main finding of this study is that a substantial number of patients with symptomatic sarcoidosis display exercise intolerance (45%), as well as muscle weakness (prevalence rates of 12–27%) and fatigue (81%). Exercise intolerance and reduced muscle strength occurred in both fatigued and nonfatigued sarcoidosis patients. Patients with impaired peripheral muscle strength were more fatigued and demonstrated impaired lung function test results, FFM, Pmax, 6MWD and QoL compared with patients without reduced peripheral muscle strength. Fatigue was neither predicted by exercise capacity, nor by muscle strength. Hamstrings peak torque accounted for only 14% of the variance of the FAS score in male patients.

Exercise intolerance was present in a substantial number of the studied sarcoidosis patients, especially in those with reduced peripheral muscle strength. In line with this, KABITZ et al. [9] also found reduced 6MWD in male sarcoidosis patients compared to healthy males. Similarly, SPRUIT et al. [5] found reduced 6MWD in sarcoidosis patients complaining of fatigue compared with healthy subjects, and ALHAMAD [7] and BAUGHMAN et al. [8] reported even lower 6MWD. The differences in 6MWD between studies were not explained by clinical characteristics. A factor that might explain differences in 6MWD in different sarcoidosis populations may be

### TABLE 2

<table>
<thead>
<tr>
<th>Summary of the physical characteristics of the sarcoidosis patients and the healthy controls studied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>6MWD m</td>
</tr>
<tr>
<td>6MWD % pred</td>
</tr>
<tr>
<td>Reduced 6MWD*</td>
</tr>
<tr>
<td><strong>Muscle force</strong></td>
</tr>
<tr>
<td>HGF lbs</td>
</tr>
<tr>
<td>HGF % pred</td>
</tr>
<tr>
<td>Reduced HGF*</td>
</tr>
<tr>
<td>EFMS N</td>
</tr>
<tr>
<td>EFMS % pred</td>
</tr>
<tr>
<td>Reduced EFMS*</td>
</tr>
<tr>
<td>QPT Nm</td>
</tr>
<tr>
<td>QPT % pred</td>
</tr>
<tr>
<td>Reduced QPT*</td>
</tr>
<tr>
<td>HPT Nm</td>
</tr>
<tr>
<td>HPT % pred</td>
</tr>
<tr>
<td>Reduced HPT*</td>
</tr>
<tr>
<td>Pmax cmH2O</td>
</tr>
<tr>
<td>Pmax % pred</td>
</tr>
<tr>
<td>Reduced Pmax*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± 2SD or %. 6MWD: 6-min walking distance; % pred: % predicted; HGF: handgrip force; EFMS: elbow flexor muscle strength; QPT: quadriceps peak torque; HPT: hamstrings peak torque; Pmax: maximal inspiratory pressure; NA: not applicable. #: percentage of subjects below the mean results minus 2SD of the control group. *: p<0.05; ***: p<0.001.
Fatigue is a prominent problem in sarcoidosis and is frequently related to an impaired QoL. Previous studies have shown a wide range of fatigue rates (30–90%) in sarcoidosis patients [2]. In the present study, muscle weakness was found in a substantial proportion of our study population, even in the absence of fatigue. Measurement of muscle strength of either the upper or lower body provided complementary information even when patients were not fatigued. The mean handgrip force and Pimax were comparable with the results reported by Spruit et al. [5], who found peripheral and Pimax impairment in sarcoidosis patients complaining of fatigue. However, the quadriceps peak torques found in the study by Spruit et al. [5] cannot be compared to those in the present study, as they measured isometric quadriceps forces, while the present study measured isokinetic quadriceps forces. Although Wirsberger et al. [11] did not find peripheral muscle weakness in sarcoidosis patients, they did find a tendency towards reduced peripheral muscle strength. The sample size of their study population was rather small. Drent et al. [4] demonstrated that fatigued patients were more likely to suffer from exercise intolerance than nonfatigued patients. Nevertheless, our study found fatigue to be only weakly related to both exercise capacity and muscle strength. Both fatigued and nonfatigued sarcoidosis patients have to cope with the complaints of reduced muscle strength and exercise intolerance. Drent et al. [4] also found reduced FFM in their studied fatigued patients. In the present study, the FFM was found to be decreased in patients with reduced peripheral muscle strength. Reduction of FFM is an expression of muscle wasting [24]. Although not directly measured in the present study, it is assumed that muscle wasting, i.e. loss of muscle bulk, might be a determinant of strength as in other chronic disorders.

Fatigue is a prominent problem in sarcoidosis and is frequently related to an impaired QoL. Previous studies have shown a wide range of fatigue rates (30–90%) in sarcoidosis patients [2].
Nevertheless, the majority of studies show fatigue prevalence rates between 70 and 90% [2]. The prevalence of fatigue in the present study was 81%. It is important to consider that most of the patients we studied were suffering from severe sarcoidosis, as this was the main reason why they were referred to a tertiary referral centre in the Netherlands.

Despite the complex and multifaceted aetiology of fatigue, several investigators have attempted to elucidate the potential causes of fatigue in sarcoidosis. Most of these studies evaluated clinical parameters, with only a few studies postulating psychological factors, such as underlying mechanisms of fatigue [25]. De Vries et al. [2] found no relationship between fatigue in sarcoidosis patients and a number of clinical variables, including pulmonary function, metabolic variables, laboratory parameters of inflammation and T-cell activation and granuloma formation. The present study investigated a multifactorial explanation of fatigue. In line with De Vries et al. [2], we did not find a relationship between fatigue and parameters commonly used to assess fatigue in sarcoidosis (demographic patient characteristics, lung function tests, radiographic stages and corticosteroid use). The aetiology of fatigue may involve general inflammation, and Drent et al. [4] found that an acute phase response (CRP levels) was associated with fatigue complaints in sarcoidosis. In the present study, however, CRP levels were unrelated to fatigue, which is in line with De Vries et al. [2]. In the present study, fatigue showed only a weak relationship with peripheral muscle strength.

Reduced exercise capacity, muscle weakness, loss of FFM and fatigue have been described in association with various chronic inflammatory diseases, such as Crohn’s disease and rheumatoid arthritis [26, 27]. Sarcoidosis patients also often present with exercise intolerance, general weakness and fatigue. The number of studies on this topic among sarcoidosis patients is limited, and most studies only included small study populations or sarcoidosis patients with specific health complaints [5, 11]. Nevertheless, the primary causes of these physical disabilities and their interrelations remain unclear for sarcoidosis too.

**Study limitations**

The present study was a cross-sectional study and, therefore, no conclusions could be drawn with regard to causality. This study only included refractory sarcoidosis patients suffering from severe physical complaints who were referred to a tertiary hospital, which may have caused selection bias. This selection might have resulted in an overestimation of the prevalence of reduced exercise capacity, muscle weakness and fatigue.

Both the 6MWT and the muscle strength tests are volitional tests. The results of these tests partially depend on the patient’s motivation and cooperation during the test. Nonvolitional testing would probably yield more valid results. However, these tests used are generally accepted in clinical studies [5, 6, 28] and, to our knowledge, sarcoidosis patients are very cooperative and motivated to participate in research projects.

In the literature, normative values for the 6MWT [29], handgrip force [16], elbow flexor muscle strength [30], and quadriceps and hamstrings peak torque [14] do exist. Our control group data are comparable with the normative values.

In conclusion, the present study showed exercise intolerance, muscle weakness and fatigue to be frequent problems in sarcoidosis. Although the majority of the patients in our study suffered from fatigue, exercise intolerance and muscle weakness occurred in both fatigued and nonfatigued patients. Patients with peripheral muscle strength impairment of the upper or lower body or both were more fatigued and demonstrated impaired lung function test results, FFM, $P_{I,max}$, 6MWD and QoL. Fatigue was not predicted by clinical parameters. More research is needed to standardise the assessment of exercise intolerance, muscle strength and fatigue in sarcoidosis. Research as to whether a multidisciplinary rehabilitation programme is of clinical benefit in the management of sarcoidosis patients is extremely necessary.

**SUPPORT STATEMENT**

This study was financially supported by a grant from the ild Care Foundation (Maastricht, the Netherlands).

**STATEMENT OF INTEREST**

None declared.

**ACKNOWLEDGEMENTS**

The authors wish to thank P. Wijnen for helping to gather and manage the data.

**REFERENCES**


---

**TABLE 4** Correlations between Fatigue Assessment Scale (FAS) scores and the absolute values of the physical characteristics of the 80 male and 44 female sarcoidosis patients studied

<table>
<thead>
<tr>
<th>FAS scores</th>
<th>6MWD</th>
<th>HGF</th>
<th>EFMS</th>
<th>QPT</th>
<th>HPT</th>
<th>$P_{I,max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.25</td>
<td>-0.25</td>
<td>-0.29</td>
<td>-0.17</td>
<td>-0.36</td>
<td>-0.24</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>-0.12</td>
<td>-0.21</td>
<td>-0.30</td>
<td>-0.04</td>
<td>-0.043</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Data are expressed as Pearson correlation (p-value). 6MWD: 6-min walking distance; HGF: handgrip force; EFMS: elbow flexor muscle strength; QPT: quadriceps peak torque; HPT: hamstrings peak torque; $P_{I,max}$: maximal inspiratory pressure.
SARCOIDOSIS

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test.