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# Predictors of fatigue in sarcoidosis: The value of exercise testing

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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 foundation 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.


## 1. 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

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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.

## 2. Material and methods

### 2.1. 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 Fig. 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.

### 2.2. Measures

#### 2.2.1. Body composition

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

#### 2.2.2. Lung function tests

Forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_1$) were measured with a pneumotachograph (Masterlab, Jaeger, Wìrzburg, Germany). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the single-breath method (Masterlab, Jaeger, Wìrzburg, Germany). Values were expressed as percentage of the predicted value (i.e., FVC %, $FEV_1$%, and DLCO %, respectively).

#### 2.2.3. 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 2-min unloaded warm-up, the intensity was increased by 25 W every 10 s, 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 $VO_2$max 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 6-min 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

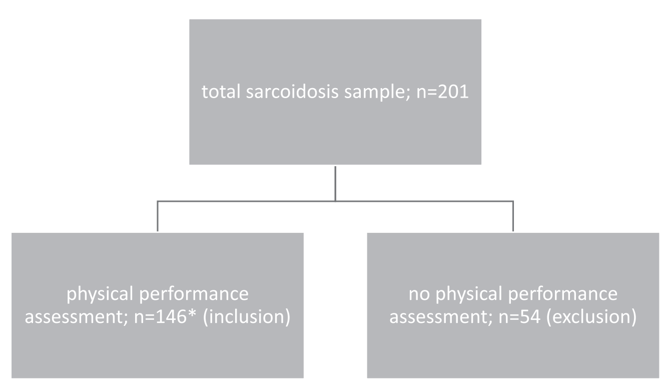


**Fig. 1.** Flowchart of the study. During the study period, data of 201 outpatients suffering from sarcoidosis were collected. At baseline, the majority of these patients (n = 146; * one excluded due to incomplete physical performance assessment) completed a physical assessment and surveys at the Department of Physical Therapy.