Is There an Added Value of Cardiopulmonary Exercise Testing in Sarcoidosis Patients?

Rik G. J. Marcellis · Antoine F. Lenssen · Geeuwke J. de Vries · Robert P. Baughman ·
Chris P. van der Grinten · Johny A. Verschakelen · Jolanda De Vries ·
Marjolein Drent

Abstract

Background Cardiopulmonary exercise testing (CPET) with blood gas analysis may be helpful when there is a discrepancy between clinical findings and physiologic tests at rest. The aim of this study was to examine the added value of CPET compared to the measurement of the diffusing capacity of the lung for carbon monoxide (DLCO) in detecting impaired pulmonary gas exchange in sarcoidosis patients.

Methods The clinical records of 160 (age = 41.3 ± 10.0 years; number of females = 63) sarcoidosis patients referred to the former MUMC ild care center were retrospectively reviewed. Patients performed a symptom-limited incremental exercise test with blood gas analysis on a bicycle ergometer. DLCO was measured by the single-breath method.

Results DLCO (mean = 83.2 ± 18.0 %) below 80 % of predicted was demonstrated by 38 % of the sarcoidosis patients in our sample. Of the patients with normal DLCO ($n = 99$, 61.9 %), the $P(A-a)O_2$ at maximal exercise [$P(A-a)O_2$max] was moderately increased (>2.5 kPa) in 69.7 % and excessively increased (>4.7 kPa) in 18.2 %. Pulmonary gas exchange impairment (PGEI) was more obvious in patients with lower DLCO values. A DLCO value below 60 % of predicted indicated substantial gas exchange impairment. PaO_2 at rest, DLCO, and FVC as a percentage of predicted and radiographic staging predicted 40 % of the PGEI at maximal exercise.

Conclusion A substantial number of the symptomatic sarcoidosis patients with normal DLCO appeared to have PGEI at maximal exercise, suggesting that normal DLCO at rest is an inappropriate predictor of abnormal pulmonary gas exchange during exercise. CPET appeared to offer added value in detecting impaired gas exchange during exercise in sarcoidosis patients with unexplained disabling symptoms.

R. G. J. Marcellis · A. F. Lenssen
Department of Physical Therapy, Maastricht University Medical
Centre (MUMC), Maastricht, The Netherlands

G. J. de Vries
Department of Respiratory Medicine, ORBIS MC,
Sittard-Geleen, The Netherlands

R. P. Baughman
University of Cincinnati Medical Center, Cincinnati, OH, USA

C. P. van der Grinten
Department of Respiratory Medicine, Maastricht University
Medical Centre (MUMC), Maastricht, The Netherlands

J. A. Verschakelen
Department of Radiology, University Hospital Gasthuisberg,
Leuven, Belgium

J. De Vries
Department of Medical Psychology, St. Elisabeth Hospital
Tilburg and Center of Research on Psychology in Somatic
Diseases (CoRPS), Tilburg University, Tilburg, The Netherlands

M. Drent (✉)
Faculty of Health, Medicine and Life Sciences, Maastricht
University, PO Box 3100, 6202 NC Maastricht, The Netherlands
e-mail: m.drent@maastrichtuniversity.nl
URL: www.ildcare.eu

M. Drent
Department of interstitial lung diseases, Gelderse Vallei
Hospital, Ede, The Netherlands

Introduction

Pulmonary disease is the most common manifestation of sarcoidosis and pulmonary symptoms are the most common reason for treatment [1–3]. Pulmonary sarcoidosis is the second-most common respiratory disease in young adults (<40 years) after asthma [1, 4, 5]. Apart from lung-related symptoms (e.g., coughing, breathlessness, and dyspnea on exertion), patients may suffer from a wide spectrum of rather nonspecific disabling symptoms like arthralgia, muscle pain, general weakness, muscle weakness, exercise limitations, fatigue, and cognitive failure [6–10]. Sarcoidosis-related symptoms may be disabling, become chronic, and affect the patients' quality of life (QOL) [7, 11, 12].

Surveillance of sarcoidosis has not been standardized. In pulmonary sarcoidosis, lung function tests and imaging methods are the most used exams during the follow-up and evaluation of the therapeutic response [1, 12–16]. A treatment philosophy of sarcoidosis is that asymptomatic patients and patients with subtle abnormalities should probably be observed rather than treated so unnecessary side effects of treatment (e.g., corticosteroid side effects) can be avoided [1]. Tools currently accepted in clinical practice to detect and follow-up respiratory functional impairment (RFI) and pulmonary gas exchange impairment (PGEI) in sarcoidosis include lung function tests at rest, including spirometry and measurement of the diffusing capacity of the lung for carbon monoxide (DLCO), and chest radiographic staging [1, 17–19]. Although these conventional tests at rest appear to be associated with an abnormal exercise test, normal spirometry and/or DLCO measurements do not exclude impaired gas exchange and exercise limitations during exercise [20]. Baughman et al. [21] and Marcellis et al. [22] demonstrated that the 6-min walk distance (6MWD) is useful to detect exercise limitations in sarcoidosis. However, in the Netherlands physical therapy reimbursement by health insurance companies depends on lung function test results at rest.

According to Miller et al. [17], PGEI in sarcoidosis patients with normal spirometry and DLCO is extremely rare. However, both Miller et al. [17] and Medinger et al. [23] reported that exercise testing might be a more sensitive way to detect impairment of oxygen transfer than DLCO in the early radiographic stages of sarcoidosis. Several other studies also discussed the value of cardiopulmonary exercise testing (CPET) for the detection of PGEI in early radiographic stages [18, 19].

It has also been suggested that CPET with blood gas analysis may be helpful, especially when there is a discrepancy between clinical findings and physiologic tests at rest [24, 25]. Recently, Lopes et al. [26] found significant reductions in forced vital capacity (FVC) and DLCO in patients with thoracic sarcoidosis at the 5-year follow-up. Additionally, they demonstrated that the outcome measures of the CPET [$P(A-a)O_2$ and breathing reserve] are predictors of a decline in pulmonary function. Although mild defects in PGEI could easily be explained by parenchymal lesions associated with sarcoidosis, the presence of persistent or progressive RFI and PGEI may indicate an increased risk of developing pulmonary hypertension or a cor pulmonale. This knowledge might influence the frequency of follow-up and treatment strategies in the management of these patients [23, 27, 28].

Therefore, the aim of the present study was to examine the possible added role of CPET compared to DLCO measurements to detect impaired pulmonary gas exchange in sarcoidosis patients with disabling symptoms. Additionally, we studied the predictive value of physical testing and other clinical characteristics, including lung function test results, radiographic stages, fatigue, dyspnea, prednisone use, and inflammatory markers, for the independent variable of impaired gas exchange.

Methods

Subjects

This retrospective study involved a review of the clinical records of 160 consecutive chronic refractory sarcoidosis patients suffering from disabling symptoms who were referred to the former ild (interstitial lung disease) care team, a tertiary referral center of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC), over a 4-year period, and who performed an exercise test with arterial blood gas analysis. The diagnosis of sarcoidosis was based on consistent clinical features and bronchoalveolar lavage fluid analysis, according to the WASOG guidelines [29], with biopsy-proven noncaseating epithelioid cell granulomas confirming sarcoidosis in 75 %. None of these patients was suffering from anemia or had another relevant medical history or comorbidity. Informed consent was obtained from all participants.

The reason for performing a CPET was unexplained disabling fatigue, complaints of dyspnea, exercise limitations, and other disabling symptoms. Disabling symptoms are defined as the presence of more than one symptom that had substantial influence on QOL and that could not be explained by the results of routine investigations, including lung function tests or chest radiographs [12]. At that time,

this test was an integral part of the diagnostic workup protocol for the patients with disabling symptoms who were referred for a second opinion. The questionnaires were completed the same day that the CPET was performed. The lung function test and chest radiographs were performed on the same day or within a week. The relevant clinical data were obtained from the medical records. This study was approved by the local Medical Ethics Committee of the MUMC.

Clinical Evaluation

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany). DLCO was measured using the single-breath method (Masterlab) [30]. Pulmonary function tests were performed according to the standards of the European Community of Coal and Steel [30].

The serum levels of soluble interleukin-2 receptor (sIL-2R) were determined using an IMMULITE Automated Analyzer [31]. The C-reactive protein (CRP) concentration was measured by a turbidimetric method on a SYNCHRON LX® (Beckman Coulter Inc., Fullerton, CA, USA) [31].

The chest radiographs [29] were scored by an experienced thoracic radiologist (JV), blinded to the patient's clinical history. Chest radiographs were graded according to DeRemee (0–III), adding stage IV [1].

Maximal Exercise Capacity and Peripheral Muscle Strength

Patients performed a symptom-limited incremental exercise test (10 W min^{-1}) on an electronically braked cycle ergometer (Cornival 400; Lode, Groningen, The Netherlands) from which peak work rate (in watts [W]) and maximal oxygen uptake (VO_2max) were determined. These exercise tests were performed according to the American Thoracic Society's standards [32]. The CPETs were interpreted by a trained and experienced physiologist (CvdG), blinded to the patient's clinical history. Pedaling frequency of between 60 and 70 cpm was chosen by the subjects and kept constant throughout the test. Breath-by-breath gas exchange was measured throughout the test using a face mask (Oxyconbeta; Jaeger, Würzburg, Germany). Arterial blood samples were taken at rest and during maximal exercise and analyzed immediately. The alveolar-arterial oxygen pressure difference (in kPa) at rest [$P(A-a)O_2$rest] and at maximal exercise [$P(A-a)O_2$max] and the difference in $P(A-a)O_2$ between rest and maximal exercise [$\Delta P(A-a)O_2$] were calculated. $P(A-a)O_2$max values above 2.5 kPa were assumed to indicate moderately

impaired gas exchange and values above 4.7 kPa indicated excessively impaired gas exchange [33, 34]. The arterial oxygen pressure and carbon dioxide pressure were also determined at rest (PaO_2rest and $PaCO_2$rest) and during maximal exercise (PaO_2max and $PaCO_2$max). PaO_2max below 10.6 kPa and $PaCO_2$ above 5.6 kPa indicated impairment [34]. Lactic acid was determined at rest and at the end of the test using the Chiron 800 series blood gas analyzer (Siemens/Chiron Diagnostics, Erlangen, Germany), which uses an electrochemical measuring chamber based on the principle of amperometry (normal value = 0.6–2.4 mmol L^{-1}). Heart rate (HR) was monitored continuously throughout the test using a 12-lead ECG. The predicted peak heart rate was calculated as 220—age [34]. Peak heart rate as a percentage of the predicted value was calculated as peak heart rate/220—age (normal value ≥85 % of the predicted value). At the end of the test, the Borg scale was used to measure perceived dyspnea (range = 1–10). CPETs were considered to be performed maximally if the lactate concentration was >4 mmol L^{-1} and/or the peak heart rate was >85 % of the predicted value at the end of the test.

Inspiratory muscle strength (Pi,max) was assessed by measuring maximal inspiratory mouth pressures at residual volume using a handheld pressure transducer (MicroMPM, Micro Medical Ltd, Rochester, UK) with a small leak [35, 36]. The maximal isometric handgrip force (HGF) of the dominant hand (in kg) was measured with a Jamar dynamometer (Sammons Preston, Chicago, IL, USA) [37].

Questionnaire

Fatigue was measured using the 10-item Fatigue Assessment Scale (FAS) questionnaire. Each item has a 5-point rating scale so FAS scores range from 10 to 50. FAS scores below 22 indicate nonfatigued persons, scores of 22–34 indicate fatigued persons, and scores of 35 or more indicate extremely fatigued persons [38]. The psychometric properties of the FAS are good, including for sarcoidosis [38].

Statistical Analysis

Demographic and clinical data are expressed as mean ± SD and, where appropriate, in absolute numbers or percentages. Frequency distributions were used to determine the prevalence of impaired lung functions, exercise intolerance, reduced muscle strength, and fatigue. The normal distribution of the variables was evaluated with the Kolmogorov-Smirnov analysis. Lung function and physical test results (peak work rate, handgrip force, and maximal inspiratory pressure) below 80 % of the predicted values were assumed to indicate physical impairment [30,

32, 36, 37]. VO_2max below 83 % of the predicted value indicated impaired exercise intolerance [32].

Patients were subdivided into three groups according to DLCO: group A (DLCO <60 % of the predicted value), group B (DLCO 60–80 % of the predicted value), and group C (DLCO ≥80 % of the predicted value). Statistically significant differences between these groups with regard to demographic, clinical, and physical characteristics were investigated by analyzing continuous data with a one-way ANOVA and examining nominal data using χ^2 tests.

Bivariate associations between P(A-a)O_2max and continuous demographic and physical characteristics were calculated using Pearson's correlations. Differences in P(A-a)O_2max values with respect to gender, oral prednisone use, and chest radiographic stages (0–I vs. II–IV) were explored by means of t-tests. Variables with a significant bivariate association with P(A-a)O_2max were used for multiple regression analysis. A backward multiple regression analysis was used to develop a model to predict P(A-a)O_2max. $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

The study included 160 symptomatic sarcoidosis patients (mean age = 41.3 ± 10.0 years). The demographic and clinical data, subdivided according to DLCO, are summarized in Table 1. The majority of the study sample were men ($n = 97$, 60.6 %).

There was a high prevalence of reduced DLCO (38.1 %) and reduced FEV_1 (35.6 %). Respiratory functional impairment (RFI; DLCO or FVC or FEV_1 <80 % of predicted) was found in 47.5 % of the sample. Patients with reduced DLCO values had more severely reduced lung function test results as well as more impaired chest radiographs compared to patients with normal DLCO values.

Exercise Intolerance

The physical characteristics of the sarcoidosis population, subdivided according to DLCO, are summarized in Table 2. Peak HR ≥85 % of the predicted value was achieved by 68 % of the patients. The peak HR was achieved by 50, 57, and 74 % in patients with a DLCO <60, 60–80, and ≥80 % of the predicted value, respectively. According to the lactate concentration and/or the peak HR at the end of the test, 83 % of the patients performed a maximal CPET. In this study, 59 % of the

patients failed to reach at least 83 % of their predicted maximal VO_2. There was a high prevalence of reduced peak work rate and VO_2max in patients with normal as well as reduced DLCO values. Patients with reduced DLCO values showed significantly poorer peak work rates and VO_2max values and more reduced peak heart rate values compared to those with normal DLCO values. PaO_2, $PaCO_2$, and P(A-a)O_2 at rest were normal compared to the reference values and did not differ between patients with normal and reduced DLCO values. Also, the difference in lactate concentrations between exercise and rest did not differ between subgroups. The mean P(A-a)O_2 at maximal exercise was increased in the total population. However, patients with reduced DLCO values showed significantly poorer P(A-a)O_2 and PaO_2 values at maximal exercise compared to those with normal DLCO values.

Peak heart rate showed weak correlations with VO_2max values ($r = 0.189$; $p = 0.018$). Fatigue (FAS score) was unrelated to the differences in lactate concentrations between rest and exercise and peak heart rate.

Gas Exchange Impairment at Maximal Exercise

P(A-a)O_2max was above 2.5 kPa in 125 patients (78.1 %) and above 4.7 kPa in 51 patients (31.9 %; see Tables 2 and 3). Slight and excessive gas exchange impairments at maximal exercise were found in 42 (89.4 %) and 20 (42.6 %) patients with a DLCO between 60 and 80 % of predicted ($n = 47$; 29.4 %), respectively, and in 69 (69.7 %) and 18 (18.2 %) patients with a normal DLCO ($n = 99$; 61.9 %; see Tables 2 and 3), respectively. None of the patients with DLCO <60 % of the predicted value had a P(A-a)O_2max below 2.5 kPa, and only one patient had a P(A-a)O_2max below 4.7 kPa (Tables 2 and 3).

Ten of 21 (47.6 %) patients with radiographic stage 0 had a P(A-a)O_2max above 2.5 kPa, and 1 of 21 (4.8 %) had a P(A-a)O_2max above 4.7 kPa. Seventeen of 25 (68.0 %) patients with radiographic stage I had a P(A-a)O_2max above 2.5 kPa, and 1 of 25 (4.0 %) had a P(A-a)O_2max above 4.7 kPa.

Of the patients ($n = 41$) with a normal DLCO value and a chest radiograph without parenchymal involvement (stages 0 and I), 23 (56.1 %) had a P(A-a)O_2max above 2.5 kPa and 2 (4.9%) had a P(A-a)O_2max above 4.7 kPa.

Muscle Weakness

Although the mean muscle strength results were normal, the prevalence of reduced handgrip force (38 %) and Pi,max (44 %) was high (Table 2). There were no significant differences in muscle strength between patients with normal and reduced DLCO values.

Table 1 Demographic and clinical characteristics of the sarcoidosis sample ($n = 160$) studied, subdivided according to DLCO

	Total sarcoidosis sample	DLCO <60 %	DLCO 60–80 %	DLCO ≥80 %
Demographics				
No. of patients (female/male)	160 (63/97)	14 (3/11)	47 (20/27)	99 (40/59)
Age (years)	41.3 ± 10.0	43.9 ± 7.2	39.8 ± 9.4	41.7 ± 10.6
Time since diagnosis (years)	4.1 ± 5.1	5.9 ± 4.9	4.7 ± 6.0	3.5 ± 4.5
Nonsmoker/smoker/given up <1 year (n)	140/17/3	13/1/0	40/6/1	87/10/2
Medication				
Prednisone use (yes/no) [n (%)][a]	81 (50.6)/79 (49.4)	10 (71.4)/4 (28.6)	31 (66.0)/16 (34.0)	40 (40.4)/59 (59.6)
Lung function tests				
DLCO (% pred)	83.2 ± 18.0	47.7 ± 6.3	70.7 ± 5.9	94.2 ± 11.3
% Reduced DLCO	38.1	100	100	0
FVC (% pred)[a,b,c]	93.9 ± 21.2	62.3 ± 11.4	83.6 ± 17.6	103.2 ± 16.8
% Reduced FVC[a,b,c]	23.1	85.7	40.4	6.1
FEV_1 (% pred)[a,b]	84.7 ± 23.6	56.6 ± 10.4	69.9 ± 21.0	95.8 ± 18.4
% Reduced FEV_1[a,b,c]	35.6	100	61.7	14.1
RFI [n (%)][a,b]	76 (47.5)	14 (100)	47 (100)	15 (15.2)
Chest radiographic stages				
0 + I versus II + III + IV [n (%)][a,b]	46 (28.8)/114 (71.2)	0 (0.0)/14 (100.0)	5 (10.6)/42 (89.4)	41 (41.4)/58 (58.6)
Inflammatory markers				
CRP <10 mg L^{-1}	13.1 ± 22.3	13.3 ± 9.4	14.5 ± 30.6	12.3 ± 18.8
sIL-2R, 214–846 kU L^{-1}	882 ± 683	1,194 ± 770	1,000 ± 641	792 ± 682
Body composition				
Body mass index (kg m^{-2})[b]	26.2 ± 4.8	23.5 ± 4.7	25.2 ± 4.6	27.0 ± 4.7
Fatigue measure				
FAS score	29.5 ± 8.2	32.1 ± 6.8	28.8 ± 7.8	29.4 ± 8.5
Fatigued (FAS ≥22) (%)	81.6	100	80.0	79.6
Extremely fatigued (FAS ≥35) (%)	30.6	42.9	25.0	31.2

Data are expressed as mean ± SD, absolute numbers, or percentages

DLCO diffusing capacity of the lung for carbon monoxide, *% pred* % of predicted value, *FVC* forced vital capacity, *FEV_1* forced expiratory volume in 1 second, *RFI* respiratory functional impairment (DLCO or FVC or FEV_1 <80 % of predicted value), *CRP* C-reactive protein, *sIL-2R* soluble interleukin-2 receptor, *FAS* fatigue assessment scale

$p < 0.05$: [a] DLCO ≥80 versus 60–80 %; [b] DLCO ≥80 versus <60 %; [c] DLCO 60–80 versus <60 %

Relationship between P(A-a)O$_2$max and Clinical Parameters

P(A-a)O$_2$max showed a moderate bivariate correlation with DLCO % (Fig. 1), FVC %, and FEV_1 %, and a weak correlation with the Borg scale and PaO$_2$rest (see, Table 4). P(A-a)O$_2$max also differed with sex ($t = 2.545$, $p = 0.012$), oral prednisone use ($t = -2.699$, $p = 0.008$), and parenchymal involvement on chest radiograph (stages 0–I vs. II–IV) ($t = -7.197$, $p < 0.001$). P(A-a)O$_2$max was not correlated with demographic characteristics (age and time since diagnosis), peak heart rate, lactate concentrations, peripheral and inspiratory muscle strength, fatigue scores, and levels of inflammatory markers (CRP and sIL2R).

Multiple regression analysis showed PaO$_2$rest, DLCO %, FVC %, and radiographic staging to be significantly independent predictors of P(A-a)O$_2$max in these patients, predicting 39.6 % of P(A-a)O$_2$max (see, Table 5).

Discussion

The aim of the present study was to evaluate the added value of CPET compared to DLCO measurements in detecting impaired pulmonary gas exchange in symptomatic sarcoidosis patients. Although 62 % of the sarcoidosis patients in our sample had normal DLCO (≥80 % of predicted), a substantial number of these patients had moderately (70 %) or even excessively (18 %) impaired pulmonary gas exchange during exercise. Chest radiographic stages without parenchymal involvement (stages 0 and I) or the absence of RFI did not exclude PGEI during exercise.

Table 2 Physical characteristics of the sarcoidosis patients ($n = 160$) studied, subdivided according to DLCO

	Total sarcoidosis sample	DLCO <60 %	DLCO 60–80 %	DLCO ≥80 %
Maximal exercise capacity				
PaO$_2$rest (kPa)	11.2 ± 1.6	10.7 ± 1.4	11.3 ± 1.8	11.2 ± 1.6
PaO$_2$max (kPa) (>10.6 kPa)[a,b,c]	11.1 ± 2.0	8.2 ± 0.6	10.6 ± 2.0	11.7 ± 1.7
ΔPaO$_2$ (kPa)[a,b,c]	−0.06 ± 2.1	−2.6 ± 1.6	−0.7 ± 2.1	0.6 ± 1.9
PaCO$_2$rest (kPa) (<5.6 kPa)	5.2 ± 0.5	5.1 ± 0.5	5.2 ± 0.5	5.2 ± 0.5
PaCO$_2$max (kPa)[a]	4.9 ± 0.7	5.2 ± 0.7	5.1 ± 0.8	4.8 ± 0.6
ΔPaCO$_2$ (kPa)[a,b]	−0.3 ± 0.7	0.1 ± 0.6	−0.1 ± 0.6	−0.4 ± 0.7
P(A-a)O$_2$rest (kPa)	2.3 ± 1.7	2.6 ± 1.5	2.3 ± 2.1	2.2 ± 1.6
P(A-a)O$_2$max (kPa)[a,b,c]	4.1 ± 1.8	6.4 ± 1.2	4.6 ± 1.7	3.5 ± 1.5
Above 2.5 kPa[a,b] (%)	78.1	100.0	89.4	69.7
Above 4.7 kPa[a,b,c] (%)	31.9	92.9	42.6	18.2
ΔP(A-a)O$_2$ (kPa)[a,b,c]	1.8 ± 2.0	4.0 ± 1.6	2.2 ± 2.0	1.2 ± 1.8
Peak power (W)				
Women	116.2 ± 30.8	87.5 ± 10.6	105.8 ± 21.3	122.9 ± 33.5
Men[a,b]	152.6 ± 51.5	100.9 ± 27.8	131.9 ± 44.9	171.8 ± 47.7
Peak power (% pred)[a,b,c]	75.6 ± 24.8	48.8 ± 15.7	69.1 ± 24.6	82.2 ± 22.8
% Reduced power[a,b]	60.4	92.3	70.2	51.5
VO$_2$ max (% pred)[a,b,c]	78.5 ± 23.9	52.4 ± 14.6	72.5 ± 23.4	85.0 ± 21.9
% Reduced VO$_2$ max[a,b,c]	59.0	100.0	68.8	48.5
Peak heart rate (beats/min)	159.1 ± 21.0	150.4 ± 20.3	154.1 ± 21.7	162.7 ± 20.0
Peak heart rate (% pred)[a]	89.0 ± 10.9	85.6 ± 12.8	85.2 ± 11.1	91.3 ± 10.1
Lactate at rest (mmol L^{-1})	1.2 ± 0.5	1.3 ± 0.6	1.2 ± 0.5	1.1 ± 0.5
Lactate at exercise (mmol L^{-1})	5.5 ± 2.0	5.1 ± 1.7	5.1 ± 1.9	5.7 ± 2.0
ΔLactate (mmol L^{-1})	4.3 ± 1.9	3.8 ± 1.8	3.9 ± 1.9	4.6 ± 1.9
Borg scale[b]	4.6 ± 2.9	6.6 ± 2.7	4.8 ± 3.2	4.2 ± 2.6
Muscle force				
HGF (kg)				
Women	26.9 ± 6.4	27.3 ± 4.2	27.4 ± 7.1	26.6 ± 6.3
Men	45.3 ± 9.8	42.4 ± 7.1	46.3 ± 9.1	45.3 ± 10.4
HGF (% pred)	86.3 ± 18.8	84.8 ± 14.9	88.5 ± 18.5	85.5 ± 19.4
% Reduced HGF	37.9	50.0	33.3	38.5
Pi,max (cmH$_2$O)				
Women	−76.2 ± 23.9	−87.3 ± 15.3	−79.0 ± 24.5	−74.0 ± 24.2
Men	−92.9 ± 28.3	−92.2 ± 33.7	−96.4 ± 31.2	−91.5 ± 26.2
Pi,max (% pred)	87.2 ± 30.1	92.8 ± 30.5	90.6 ± 33.9	84.8 ± 28.1
% Reduced Pi,max	43.9	35.7	44.4	44.8

Data are expressed as mean ± SD or percentages. Reference values are in parenthesis

PaO$_2$ arterial oxygen pressure, *Δ* change in oxygen or carbon dioxide pressure or lactate concentration between rest and maximal exercise, *PaCO$_2$* arterial carbon dioxide pressure, *P(A-a)O$_2$* alveolar-arterial oxygen pressure difference, *% pred* % of predicted value, *HGF* handgrip force, *Pi,max* maximal inspiratory pressure

$p < 0.05$: [a] DLCO ≥80 % versus 60–80 %; [b] DLCO ≥80 % versus <60 %; [c] DLCO 60–80 % versus <60 %

P(A-a)O$_2$max was not correlated with demographic characteristics, peak heart rate, lactate concentrations, peripheral and inspiratory muscle strength, fatigue scores, and levels of inflammatory markers (CRP and sIL2R). PaO$_2$ at rest, DLCO %, FVC %, and radiographic staging predicted only 40 % of P(A-a)O$_2$max, so a normal DLCO as well as normal spirometry or a chest radiograph stage without signs of parenchymal involvement appeared to be inappropriate predictors of PGEI during exercise and did not rule out abnormalities in pulmonary gas exchange.

Sarcoidosis patients often present with nonspecific health complaints. Chronic fatigue related to exercise intolerance is a common symptom of patients with sarcoidosis [39]. In agreement with other research findings,

Table 3 Frequency distribution of the alveolar-arterial oxygen pressure difference at maximal exercise (cutoff values: 2.5 and 4.7 kPa) for each of the three DLCO groups

	DLCO <60 %	DLCO 60–80 %	DLCO ≥80 %	Total sarcoidosis sample
P(A-a)O$_2$max ≤2.5 kPa	0	5	30	35
P(A-a)O$_2$max >2.5–4.7 kPa	1	22	51	74
P(A-a)O$_2$max >4.7 kPa	13	20	18	51
	14	47	99	160

Data are expressed as absolute numbers

DLCO diffusing capacity of the lung for carbon monoxide, *P(A-a)O$_2$max* alveolar-arterial oxygen pressure difference at maximal exercise
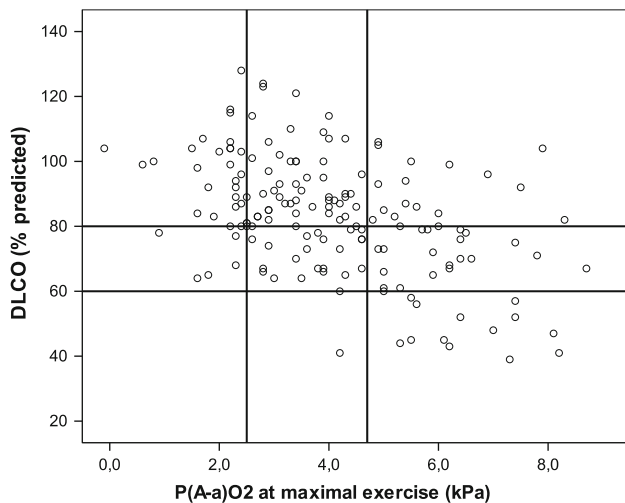

Fig. 1 Correlation of the resting single-breath DLCO expressed as percentage of the predicted value and the alveolar-arterial oxygen pressure difference [P(A-a)O$_2$] at maximal exercise ($r = -0.48$, $p < 0.001$). The figure includes cutoff values for both DLCO (60 and 80 %, respectively) and P(A-a)O$_2$ at maximal exercise (2.5 and 4.7 kPa, respectively)

Table 4 Correlations between alveolar-arterial oxygen pressure difference at maximal exercise [P(A-a)O$_2$max] and patients' pulmonary and physical characteristics

Variables	Pearson's correlation coefficient (r)	p value
DLCO (% pred)	−0.475	<0.001
FVC (% pred)	−0.468	<0.001
FEV$_1$ (% pred)	−0.465	<0.001
FAS score	−0.060	0.474
Modified Borg scale	0.271	0.001
PaO$_2$rest (kPa)	−0.315	<0.001

DLCO diffusing capacity of the lung for carbon monoxide, *% pred* % of predicted value, *FVC* forced vital capacity, *FEV$_1$* forced expiratory volume in one second, *FAS* fatigue assessment scale, *PaO$_2$* arterial oxygen pressure

impaired pulmonary functions, peak inspiratory mouth pressures, and 6MWD [22]. The results of the present study are in agreement with those of previous studies, demonstrating a reduction in VO$_2$max in sarcoidosis [42]. Exercise intolerance in sarcoidosis is most often multifactorial, involving, for instance, lung-mechanical, musculoskeletal, and gas exchange abnormalities [43]. Several studies have reported that neither lung function test results nor chest radiographs correlate with these nonspecific health complaints, nor with QOL [21, 22, 41, 44]. Our study results are in agreement with those of Wallaert et al. [42], who showed pulmonary function test results at rest to be poor predictors of exercise capacity. In contrast to our study, Wallaert et al. [42] showed a moderate correlation between VO$_2$max and peak HR. In line with Ingram et al. [45], the present study also found that both DLCO and chest radiographs at rest appeared to be insensitive predictors of PGEI during exercise. Moreover, five of 47 (11 %) patients with a DLCO below 80 % of predicted had a chest radiographic stage 0 or I.

Exercise testing is a useful tool that provides valuable diagnostic and prognostic information about patients with pulmonary diseases [46]. The importance of exercise testing in evaluating PGEI in sarcoidosis and various other diffuse lung diseases has been demonstrated, as pulmonary gas exchange problems that are not obvious at rest often become apparent during exercise [20, 24, 25]. In line with the present study, Lopes et al. [26] demonstrated that the outcome measure P(A-a)O$_2$ of the CPET was a predictor of a decline in pulmonary function in a sarcoidosis population with rather severe thoracic sarcoidosis. They concluded that determining the CPET measures may be helpful in predicting the outcomes of patients with thoracic sarcoidosis. Obviously, in the study by Lopes et al. [26] mainly patients with severe pulmonary involvement were included. This might explain the higher correlation between P(A-a)O$_2$ and the pulmonary functions compared with the results of our study (see, Table 4).

The present study also showed PGEI in patients with normal spirometry, as had also been observed by Kollert et al. [47]. Although abnormal gas exchange during exercise was rare in patients with normal spirometry and

Marcellis et al. [22] recently showed that exercise intolerance assessed by the 6-min walk test and muscle weakness are rather common in sarcoidosis patients [40, 41]. Those with decreased limb muscle strength exhibited

Table 5 Multiple regression analysis: relationship between the alveolar-arterial oxygen pressure difference at maximal exercise and clinical variables

Outcome variable	Independent variables	Unstandardized coefficient		Standardized coefficients	*p* value
		B	Std error	Beta	
P(A-a)O$_2$max (kPa)	(constant)	10.42	1.091		<0.001
	DLCO (% pred)	−0.028	0.008	−0.291	0.001
	FVC (% pred)	−0.016	0.007	−0.194	0.029
	PaO$_2$rest (kPa)	−0.274	0.072	−0.255	<0.001
	Chest radiographic stages (0–I vs. II–IV)	0.700	0.278	0.181	0.013

P(A-a)O$_2$max alveolar-arterial oxygen pressure difference at maximal exercise, *DLCO* diffusing capacity of the lung for carbon monoxide, *% pred* % of predicted value, *FVC* forced vital capacity, *PaO$_2$* arterial oxygen pressure

normal DLCO in the study by Miller et al. [17], they stressed that exercise testing could play a role in demonstrating occult PGEI. Medinger et al. [23] and Athos et al. [19] also demonstrated that CPET with blood gas analysis was useful in detecting abnormal gas exchange in early radiographic stages of sarcoidosis.

In contrast to the present study, Barros et al. [18] did not find PGEI in patients with radiographic stages 0 and I during moderate exercise. Their research found a 27 % prevalence of PGEI in sarcoidosis patients with radiographic stages II–IV. In our study, the prevalence of PGEI was higher in the more advanced radiographic stages II–IV. However, these studies used different criteria to define PGEI. Lopes et al. [13] also showed an abnormally increased PGEI in the more advanced HRCT stages.

In accordance with the findings of Barros et al. [18], a DLCO below 60 % of predicted was indicative of PGEI in our study. Although we did find that a low DLCO predicted PGEI, we found a significant number of patients with a normal DLCO who still had PGEI. A DLCO below 60 % of predicted is also a predictor of sarcoidosis-associated pulmonary hypertension (SAPH) [27], which is associated with increased mortality [48]. However, DLCO was not as sensitive or specific as the 6-min walk test results [27]. A significant proportion of dyspneic sarcoidosis patients will have pulmonary hypertension, and CPET may also show impaired gas exchange in SAPH [48]. Exercise testing may prove more sensitive in screening for pulmonary hypertension. Our cross-sectional study design made it impossible to determine which patients went on to develop pulmonary hypertension. We do know that some patients with PGEI had a lung transplant or died a few years later. A prospective study with baseline and follow-up data is needed to identify more severe consequences of sarcoidosis and those who might be at risk of developing SAPH, and to evaluate the added value of CPET compared with the usefulness of the 6-min walk test in this regard.

A symptom-limited incremental exercise test is a volitional test and can be influenced by the patient's motivation and will power. This has also been observed in studies using the 6MWD [21]. However, the test we used is generally accepted in clinical studies. In our experience, sarcoidosis patients are highly motivated and are willing to participate in all kinds of studies, including an exercise test.

In conclusion, normal DLCO and spirometry and a chest radiograph without parenchymal involvement did not rule out abnormalities in pulmonary gas exchange at maximal exercise in symptomatic sarcoidosis patients. Surveillance of sarcoidosis has still not been standardized, as no single measurement appeared to be sufficient to assess pulmonary disease severity. CPET could offer added value in detecting PGEI during exercise for symptomatic patients with normal spirometry and chest radiography without parenchymal involvement. CPET might also be useful for detecting early parenchymal involvement in sarcoidosis. Hence, CPET with blood gas analysis should be considered an integral part of the multidisciplinary management of sarcoidosis patients with unexplained disabling symptoms aimed to guide appropriate treatment including physical therapy.

References

1. No authors listed (1999) 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 160(2): 736–755

2. Baughman RP, Culver DA, Judson MA (2011) A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med 183(5):573–581

3. Baughman RP, Nunes H (2012) Therapy for sarcoidosis: evidence-based recommendations. Expert Rev Clin Immunol 8(1):95–103

4. Morgenthau AS, Iannuzzi MC (2011) Recent advances in sarcoidosis. Chest 139(1):174–182

5. Iannuzzi MC, Rybicki BA, Teirstein AS (2007) Sarcoidosis. N Engl J Med 357(21):2153–2165

6. Wirnsberger RM, de Vries J, Wouters EF, Drent M (1998) Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. Neth J Med 53(2):53–60

7. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J (2006) Fatigue is associated with quality of life in sarcoidosis patients. Chest 130(4):989–994

8. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M (2010) Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. Respiration 80:212–219

9. Korenromp IH, Heijnen CJ, Vogels OJ, van den Bosch JM, Grutters JC (2011) Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. Chest 140(2):441–447

10. Baydur A, Alavy B, Nawathe A, Liu S, Louie S, Sharma OP (2011) Fatigue and plasma cytokine concentrations at rest and during exercise in patients with sarcoidosis. Clin Respir J 5(3):156–164

11. Drent M, Lower EE, De Vries J (2012) Sarcoidosis-associated fatigue. Eur Respir J 40(1):255–263

12. Mostard RL, Voo S, van Kroonenburgh MJ, Verschakelen JA, Wijnen PA, Nelemans PJ, Erckens RJ, Drent M (2011) Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. Respir Med 105(12):1917–1924

13. Lopes AJ, de Menezes SL, Dias CM, de Oliveira JF, Mainenti MR, Guimaraes FS (2011) Comparison between cardiopulmonary exercise testing parameters and computed tomography findings in patients with thoracic sarcoidosis. Lung 189(5):425–431

14. Gafa G, Sverzellati N, Bonati E et al (2012) Follow-up in pulmonary sarcoidosis: comparison between HRCT and pulmonary function tests. Radiol Med 117(6):968–978

15. Erdal BS, Crouser ED, Yildiz V, King MA, Patterson AT, Knopp MV, Clymer BD (2012) Quantitative computerized two-point correlation analysis of lung CT scans correlates with pulmonary function in pulmonary sarcoidosis. Chest doi: 10.1378/chest.11-2027

16. Nunes H, Uzunhan Y, Gille T, Lamberto C, Valeyre D, Brillet PY (2012) Imaging of sarcoidosis of the airways and lung parenchyma with correlation with lung function. Eur Respir J 40(3):750–765

17. Miller A, Brown LK, Sloane MF, Bhuptani A, Teirstein AS (1995) Cardiorespiratory responses to incremental exercise in sarcoidosis patients with normal spirometry. Chest 107(2):323–329

18. Barros WG, Neder JA, Pereira CA, Nery LE (2004) Clinical, radiographic and functional predictors of pulmonary gas exchange impairment at moderate exercise in patients with sarcoidosis. Respiration 71(4):367–373

19. Athos L, Mohler JG, Sharma OP (1986) Exercise testing in the physiologic assessment of sarcoidosis. Ann N Y Acad Sci 465:491–501

20. Karetzky M, McDonough M (1996) Exercise and resting pulmonary function in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 13(1):43–49

21. Baughman RP, Lower EE (2007) Six-minute walk test in managing and monitoring sarcoidosis patients. Curr Opin Pulm Med 13(5):439–444

22. Marcellis RG, Lenssen AF, Elfferich MD, De Vries J, Kassim S, Foerster K, Drent M (2011) Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J 38(3):628–634

23. Medinger AE, Khouri S, Rohatgi PK (2001) Sarcoidosis: the value of exercise testing. Chest 120(1):93–101

24. Risk C, Epler GR, Gaensler EA (1984) Exercise alveolar-arterial oxygen pressure difference in interstitial lung disease. Chest 85(1):69–74

25. Bradvik I, Wollmer P, Blom-Bulow B, Albrechtsson U, Jonson B (1991) Lung mechanics and gas exchange during exercise in pulmonary sarcoidosis. Chest 99(3):572–578

26. Lopes AJ, Menezes SL, Dias CM, Oliveira JF, Mainenti MR, Guimaraes FS (2012) Cardiopulmonary exercise testing variables as predictors of long-term outcome in thoracic sarcoidosis. Braz J Med Biol Res 45(3):256–263

27. Bourbonnais JM, Samavati L (2008) Clinical predictors of pulmonary hypertension in sarcoidosis. Eur Respir J 32(2):296–302

28. Corte TJ, Wells AU, Nicholson AG, Hansell DM, Wort SJ (2011) Pulmonary hypertension in sarcoidosis: a review. Respirology 16(1):69–77

29. Hunninghake GW, Costabel U, Ando M et al (1999) ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis 16(2):149–173

30. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC (1993) Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 16:5–40

31. Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PG, Drent M (2003) Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. Clin Chem 49(9):1510–1517

32. American College of Chest Physicians, American Thoracic Society (2003) ATS/ACCP Statement on cardiopulmonary exercise testing. Joint Statement of the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP) was adopted by the ATS Board of Directors and by the ACCP Health Science Policy Committee, November 1, 2001. Am J Respir Crit Care Med 167(2):211–277

33. Warrell DA, Cox TM, Firth JD, Benz EJ (2005) Oxford textbook of medicine, 4th edn. Oxford University Press, New York

34. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ (2005) Principles of exercise testing and interpretation, 4th edn. Lippincott Williams & Wilkins, Philadelphia

35. Black LF, Hyatt RE (1969) Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis 99:696–702

36. Harik-Khan RI, Wise RA, Fozard JL (1998) Determinants of maximal inspiratory pressure. The baltimore longitudinal study of aging. Am J Respir Crit Care Med 158(5 Pt 1):1459–1464

37. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S (1985) Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil 66(2):69–74

38. Michielsen HJ, De Vries J, Van Heck GL, Van de Vijver FJR, Sijtsma K (2004) Examination of the dimensionality of fatigue: the construction of the fatigue assessment scale (FAS). Eur J Psychol Assess 20(1):39–48

39. Baydur A (2012) Recent developments in the physiological assessment of sarcoidosis: clinical implications. Curr Opin Pulm Med 18(5):499–505

40. Spruit MA, Thomeer MJ, Gosselink R, Troosters T, Kasran A, Debrock AJ, Demedts MG, Decramer M (2005) Skeletal muscle weakness in patients with sarcoidosis and its relationship with

exercise intolerance and reduced health status. Thorax 60(1): 32–38

41. Wirnsberger RM, Drent M, Hekelaar N, Breteler MH, Drent S, Wouters EF, Dekhuijzen PN (1997) Relationship between respiratory muscle function and quality of life in sarcoidosis. Eur Respir J 10(7):1450–1455

42. Wallaert B, Talleu C, Wemeau-Stervinou L, Duhamel A, Robin S, Aguilaniu B (2011) Reduction of maximal oxygen uptake in sarcoidosis: relationship with disease severity. Respiration 82(6):501–508

43. Sietsema KE, Kraft M, Ginzton L, Sharma OP (1992) Abnormal oxygen uptake responses to exercise in patients with mild pulmonary sarcoidosis. Chest 102(3):838–845

44. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M (2004) The relationship between fatigue and clinical parameters

in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 21(2):127–136

45. Ingram CG, Reid PC, Johnston RN (1982) Exercise testing in pulmonary sarcoidosis. Thorax 37(2):129–132

46. Arena R, Sietsema KE (2011) Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. Circulation 123(6):668–680

47. Kollert F, Geck B, Suchy R et al (2011) The impact of gas exchange measurement during exercise in pulmonary sarcoidosis. Respir Med 105(1):122–129

48. Palmero V, Sulica R (2010) Sarcoidosis-associated pulmonary hypertension: assessment and management. Semin Respir Crit Care Med 31(4):494–500