# Chapter 5

## Is there an added value of cardiopulmonary exercise testing in sarcoidosis patients?

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# 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 Maastricht University Medical Centre (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 $P(A\text{-}a)O_2$ at maximal exercise ($P(A\text{-}a)O_2max$) 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.

## 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-minute walking 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 ($P(A\text{-}a)O_2$ 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 World Association of Sarcoidosis and Other Granulomatous Disorders (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 one 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) on an electronically braked cycle ergometer (Cornival 400, Lode, Groningen, the Netherlands) from which peak work rate (in watts (W)) and maximal oxygen uptake ($VO_2$max) 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 ($P(A\text{-}a)O_2$rest) and at maximal exercise ($P(A\text{-}a)O_2$max) and the difference in $P(A\text{-}a)O_2$ between rest and maximal exercise ($\Delta P(A\text{-}a)O_2$) were calculated. $P(A\text{-}a)O_2$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 ($PaO_2$rest and $PaCO_2$rest) and during maximal exercise ($PaO_2$max and $PaCO_2$max). $PaO_2$max 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). 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 and/or the peak heart rate was >85% of the predicted value at the end of the test.

Inspiratory muscle strength (PImax) 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 ± standard deviation (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] $VO_2$max 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 $\chi^2$ tests.

Bivariate associations between P(A-a)$O_2$max and continuous demographic and physical characteristics were calculated using Pearson's correlations. Differences in P(A-a)$O_2$max 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)$O_2$max were used for multiple regression analysis. A backward multiple regression analysis was used to develop a model to predict P(A-a)$O_2$max. $p<0.05$ 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 5.1. 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.

Table 5.1 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 (yrs) | 41.3 ± 10.0 | 43.9 ± 7.2 | 39.8 ± 9.4 | 41.7 ± 10.6 |
| Time since diagnosis (yrs) | 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) / 14 (100.0) | 5 (10.6) / 42 (89.4) | 41 (41.4) / 58 (58.6) |
| Inflammatory markers | | | | |
| CRP <10 mg/l | 13.1 ± 22.3 | 13.3 ± 9.4 | 14.5 ± 30.6 | 12.3 ± 18.8 |
| sIL-2R, 214-846 kU/l | 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 | 5.2 ± 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 ± standard deviation (SD), absolute numbers (n), 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 one 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%.

## Exercise intolerance

The physical characteristics of the sarcoidosis population, subdivided according to DLCO, are summarized in Table 5.2. 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 $VO_2$max in patients with normal as well as reduced DLCO values. Patients with reduced DLCO values showed significantly poorer peak work rates and $VO_2$max 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 $VO_2$max 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)$O_2$max was above 2.5 kPa in 125 patients (78.1%) and above 4.7 kPa in 51 patients (31.9%; Tables 5.2 and 5.3). 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%; Tables 5.2 and 5.3), respectively. None of the patients with DLCO <60% of the predicted value had a P(A-a)$O_2$max below 2.5 kPa, and only one patient had a P(A-a)$O_2$max below 4.7 kPa (Tables 5.2 and 5.3).

Ten of 21 (47.6%) patients with radiographic stage 0 had a P(A-a)$O_2$max above 2.5 kPa, and 1 of 21 (4.8%) had a P(A-a)$O_2$max above 4.7 kPa. Seventeen of 25 (68.0%) patients with radiographic stage I had a P(A-a)$O_2$max above 2.5 kPa, and 1 of 25 (4.0%) had a P(A-a)$O_2$max 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)$O_2$max above 2.5 kPa and 2 (4.9%) had a P(A-a)$O_2$max above 4.7 kPa.

Table 5.2 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 |
| Δ$PaO_2$ (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 |
| Δ$PaCO_2$ (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 |
| Δ P(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) | 1.2 ± 0.5 | 1.3 ± 0.6 | 1.2 ± 0.5 | 1.1 ± 0.5 |
| Lactate at exercise (mmol/) | 5.5 ± 2.0 | 5.1 ± 1.7 | 5.1 ± 1.9 | 5.7 ± 2.0 |
| ΔLactate (mmol/l) | 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 |
| PImax ($cmH_2O$) | | | | |
| 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 |
| PImax (% pred) | 87.2 ± 30.1 | 92.8 ± 30.5 | 90.6 ± 33.9 | 84.8 ± 28.1 |
| % Reduced PImax | 43.9 | 35.7 | 44.4 | 44.8 |

Data are expressed as mean ± standard deviation (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; PImax: maximal inspiratory pressure. p<0.05: [a] DLCO ≥80% versus 60-80%; [b] DLCO ≥80% versus <60%; [c] DLCO 60-80% versus <60%.

## Muscle weakness

Although the mean muscle strength results were normal, the prevalence of reduced handgrip force (38%) and PImax (44%) was high (Table 5.2). There were no significant differences in muscle strength between patients with normal and reduced DLCO values.

Table 5.3 Frequency distribution of the alveolar-arterial oxygen pressure difference at maximal exercise (cutoff values: 2.5 kPa 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.

## Relationship between P(A-a)$O_2$max and clinical parameters

P(A-a)$O_2$max showed a moderate bivariate correlation with DLCO% (Figure 5.1), FVC%, and $FEV_1$%, and a weak correlation with the Borg scale and $PaO_2$rest (Table 5.4).
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 sIL-2R).

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 (Table 5.5).

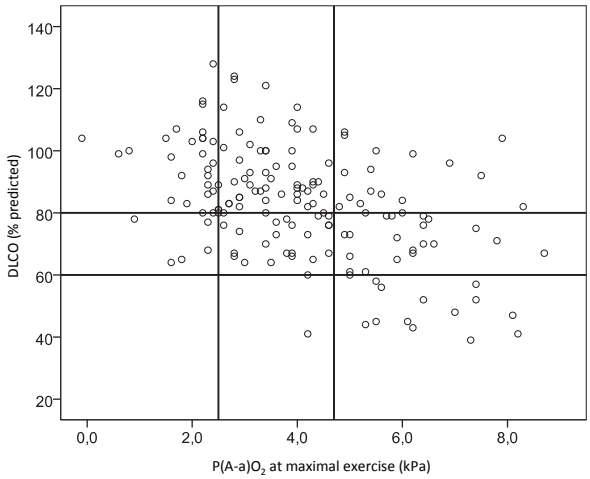


Figure 5.1 Correlation of the resting single-breath DLCO expressed as percentage of the predicted value and the alveolar-arterial oxygen pressure difference (P(A-a)$O_2$) at maximal exercise (r=-0.48, p<0.001). The figure includes cutoff values for both DLCO (60% and 80%, respectively) and P(A-a)$O_2$ at maximal exercise (2.5 kPa and 4.7 kPa, respectively).

Table 5.4 Correlations between alveolar-arterial oxygen pressure difference at maximal exercise ($P(A\text{-}a)O_2max$) 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.

Table 5.5 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 | |
| $P(A\text{-}a)O_2max$ (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 |

$P(A\text{-}a)O_2max$: 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.

## 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.

$P(A\text{-}a)O_2max$ 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 sIL-2R). $PaO_2$ at rest, DLCO%, FVC%, and radiographic staging predicted only 40% of $P(A\text{-}a)O_2max$, 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, Marcellis *et al*.[22] recently showed that exercise intolerance assessed by the 6-minute walk test and muscle weakness are rather common in sarcoidosis patients.[40,41] Those with decreased limb muscle strength exhibited 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 $P(A\text{-}a)O_2$ 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 $P(A\text{-}a)O_2$ and the pulmonary functions compared with the results of our study (Table 5.4).

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 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-minute 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-minute 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.

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