Oxygen desaturation during a 6-minute walk test as a predictor of maximal exercise-induced gas exchange abnormalities in sarcoidosis

Cecile Chenivesse 1*, Sarah Boulanger 1*, Carole Langlois 2, Lidwine Wemeau-Stervinou 1, Thierry Perez 1,3, Benoit Wallaert 1

1Department of Respiratory Medicine, Rare Disease Center, 2Department of Biostatistics, 3Lung Function Department, Univ. Lille, F-59000 Lille, France

Contributions: (I) Conception and design: C Chenivesse, S Boulanger, C Langlois, L Wemeau-Stervinou, B Wallaert; (II) Administrative support: None; (III) Provision of study materials or patients: S Boulanger, C Langlois, L Wemeau-Stervinou, T Perez, B Wallaert; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Benoit Wallaert. Department of Respiratory Medicine, Rare Disease Center, CHU Lille, University Hospital of Lille, Boulevard Jules Leclercq, F-59000, Lille, France. Email: benoit.wallaert@chru-lille.fr.

Background: Common tests for evaluating gas exchange impairment have different strengths and weaknesses. Alveolar-to-arterial oxygen pressure difference (AaDO2) at peak exercise is a sensitive indicator but it cannot be measured repeatedly. Diffusing capacity of the lung for carbon monoxide (DLco) is measured at rest and may be too insensitive to predict the effects of exercise on gas exchange impairment. Oxygen desaturation during a 6-minute walk test (ΔSpO2-6MWT) can be measured repeatedly, but its value in sarcoidosis is unknown. Here, we evaluated the ability of ΔSpO2-6MWT and DLco to predict gas exchange impairment during exercise in sarcoidosis.

Methods: This retrospective study of 130 subjects with sarcoidosis investigated the relationship between DLco, ΔSpO2-6MWT, and peak AaDO2 using correlation tests, inter-test reliability analyses, and predictive values. For the analyses of inter-test reliability and predictive values, DLco, peak AaDO2, and ΔSpO2-6MWT were considered as binary variables (normal/abnormal) according to previously defined thresholds.

Results: Correlation coefficients between DLco, ΔSpO2-6MWT, and peak AaDO2 were intermediate (0.53–0.67, P<0.0003) and Kappa coefficients were low (0.21–0.42, P=0.0003–0.02). DLco predicted (I) increased peak AaDO2 with a positive predictive value (PPV) of 66% and a negative predictive value (NPV) of 78% and (II) increased ΔSpO2-6MWT with a PPV at 36% and an NPV at 88%. Normal DLco was a good predictor of the absence of severe desaturation during the 6MWT (94% NPV) and at peak exercise during cardiopulmonary exercise test (CPET) (100% NPV). ΔSpO2-6MWT predicted peak AaDO2 increase with a PPV of 74% and an NPV of 60%.

Conclusions: In a large population of sarcoidosis patients, neither ΔSpO2-6MWT nor DLco was a good predictor of increased peak AaDO2. In contrast, normal DLco was a good predictor of the absence of severe desaturation during the 6MWT and at peak exercise during CPET.

Keywords: Sarcoidosis; pulmonary gas exchange; 6-minute walk test (6MWT); alveolar-arterial oxygen gradient; cardiopulmonary exercise test (CPET); diffusing capacity

Submitted Apr 22, 2016. Accepted for publication May 11, 2016.
doi: 10.21037/jtd.2016.06.39
View this article at: http://dx.doi.org/10.21037/jtd.2016.06.39
Introduction

Sarcoidosis is a systemic granulomatous disorder preferentially involving the lung. Pulmonary sarcoidosis is usually benign. Although gas exchange measurements in interstitial lung disease usually include the diffusing capacity of the lung for carbon monoxide (DLco), it is unclear whether estimates of gas exchange might be improved by measuring oxygen desaturation ($\Delta$SpO$_2$) during a 6-minute walk test (6MWT) and/or the alveolar-to-arterial oxygen pressure difference measured at peak exercise (peak AaDO$_2$) during a cardiopulmonary exercise test (CPET) (1-5). On the one hand, peak AaDO$_2$ is more sensitive than DLco (3,6,7), but CPET requires time and equipment and is challenging for sarcoidosis patients (8), limiting its use for systematic initial evaluation and for routine monitoring (9). On the other hand, $\Delta$SpO$_2$ during a 6MWT ($\Delta$SpO$_2$-6MWT) is a measure of gas exchange at exercise and is a simple, reproducible, and well-tolerated exam (10), which are advantages for sarcoidosis evaluation (11). Measurement of $\Delta$SpO$_2$-6MWT as performed in the present study has recently been added to the international guidelines for walking tests (12). Although this test has not been investigated extensively, it is reproducible (13) and correlates with symptom intensity (14), results of pulmonary function testing (15), changes on computed tomography (CT) scans (16), and prognosis (17-19) in interstitial lung diseases. However, the correlation between $\Delta$SpO$_2$-6MWT and peak AaDO$_2$ and, in particular, the ability of $\Delta$SpO$_2$-6MWT to predict peak AaDO$_2$, are unknown. In the present study, we investigated in a large population of sarcoidosis patients the relationship between DLco and two other indicators of gas exchange; namely, $\Delta$SpO$_2$-6MWT and peak AaDO$_2$, using correlation and inter-test agreement tests and evaluated the ability of $\Delta$SpO$_2$-6MWT and DLco to predict gas exchange impairment during exercise in sarcoidosis.

Methods

Subjects and study design

We conducted a monocentric retrospective study of 130 subjects. All sarcoidosis patients referred to our tertiary respiratory care clinic over a period of 6 years were considered for inclusion. Subjects were included if the diagnosis of sarcoidosis was histologically proved and if they had performed a 6MWT and a CPET with blood gas measurement at peak exercise on the same day. Exercise tests were performed either at the time of diagnosis or during the course of the disease. If a patient had performed multiple tests, the first complete evaluation was selected for analysis. Demographic, clinical, radiological, and functional data, including pulmonary function tests, 6MWT, and CPET, were recorded. The relationships between DLco, $\Delta$SpO$_2$-6MWT, and peak AaDO$_2$ were analyzed.

Sarcoidosis classification

Pulmonary sarcoidosis was classified into five stages according to the ERS/ATS statement on sarcoidosis as follows: stage 0, no visible intrathoracic findings; stage I, bilateral hilar adenopathy; stage II, bilateral hilar adenopathy and parenchymal infiltration; stage III, parenchymal infiltration without hilar adenopathy; and stage IV, evidence of pulmonary fibrosis with cicatricial changes (9).

Pulmonary function tests

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV$_1$), and total lung capacity (TLC) were measured by spirometry and plethysmography (Jaeger-Masterlab$^\text{®}$). Single-breath DLco was measured. The DLco value was adjusted for hemoglobin by applying Cotes’ equation: adjusted DLco = $\frac{\text{DLco} \times (10.2 + \text{hemoglobin})}{1.7 \times \text{hemoglobin}}$. Predicted values for lung volumes and DLco were based on the ERS statement (20,21). DLco was considered normal if it was above the lower limit of normal (LLN), defined as the 5th percentile (22). Resting arterial blood gas tensions were measured on room air. Normal values for resting partial pressure of oxygen (PaO$_2$) and AaDO$_2$ were derived from the literature (23,24).

6MWT

The 6MWT was performed in accordance with international recommendations (10). Peripheral capillary oxygen saturation (SpO$_2$) was monitored continuously using a handheld oximeter (Nellcor OxiMax$^\text{®}$ N-65). $\Delta$SpO$_2$-6MWT was defined as the difference between the resting and nadir SpO$_2$. A desaturation $\geq$4% was considered significant (25).

CPET

CPET was performed to investigate dyspnea in 85 patients
SpO2 <90% during the 6MWT and PaO2 <60 mmHg at thresholds characteristic of severe hypoxemia (nadir the previously defined threshold and second according and PPV, respectively) were calculated, first according to intervals. Negative and positive predictive values (NPV using the Kappa coefficient test with 95% confidence ≥ 4%, peak AaDO2 >30 mmHg). Concordance between the quantitative variables DLco, AaDO2-6MWT, and peak AaDO2 in the whole population were evaluated using a bivariate Pearson test. Inter-test reliability, predictive values, and ROC curves were derived using DLco, AaDO2-6MWT, and peak AaDO2 as binary qualitative variables (normal vs. abnormal) according to the thresholds stated above (DLco < LLN, AaDO2-6MWT ≥4%, peak AaDO2 >30 mmHg). Concordance between DLco, AaDO2-6MWT, and peak AaDO2 was evaluated using the Kappa coefficient test with 95% confidence intervals. Negative and positive predictive values (NPV and PPV, respectively) were calculated, first according to the previously defined threshold and second according to thresholds characteristic of severe hypoxemia (nadir SpO2 <90% during the 6MWT and PaO2 <60 mmHg at peak exercise during CPET). ROC curves were calculated to determine whether more relevant thresholds could be identified. A correction for multiplicity was applied to descriptive results, correlation tests, and Kappa coefficients using the Benjamini-Hochberg procedure. A P value <0.05 was considered significant.

Results

Subjects

One hundred and thirty subjects were included. The population consisted of 52 women (40%) and 78 men (60%), of whom 114 were Caucasians (87%) and 16 were Africans (13%). The mean ± SD age was 49±11 years (range, 26–78 years) and the mean body mass index was 27 kg·m−2. Sixty percent of the population had no smoking history, 15% were active smokers, and 25% were ex-smokers. Pulmonary sarcoidosis was classified as stage I in 11 subjects (8.5%), stage II in 69 subjects (53%), stage III in 11 subjects (8.5%), and stage IV in 39 subjects (30%). At the time of functional exercise testing, the proportion of subjects receiving corticosteroids was 10% of stage I subjects, 44% of stage II subjects, 36% of stage III subjects, and 76% of stage IV subjects. The proportion of steroid treatment was significant differences between all groups.

Physiological evaluation

Pulmonary function tests, AaDO2, at rest and peak exercise, and 6MWT results are detailed in Table 1. In summary, the stage IV sarcoidosis group had lower FEV1, FVC, FEV1/FVC, DLco, peak oxygen uptake (VO2 peak), and peak PaO2 and higher AaDO2 than the stage I, II, and III groups. There were no significant differences in these variables between stage I, II, and III groups. ΔSpO2-6MWT was higher in the stage IV group than in stage II and III groups, and higher in the stage II group than in the stage III group. The prevalence of obstructive and restrictive ventilatory defects was similar to those previously published (1,7,28), and was 23% for airway obstruction (FEV1/FVC < LLN), 21% for airway restriction (TLC <80% of predicted value), and 61.5% for decreased DLco (DLco < LLN). Resting PaO2 and AaDO2 were considered abnormal according to literature normal values (23,24) in 40% and 30% of cases, respectively. In most of these abnormal cases, the parameters were not markedly altered (25th percentile PaO2 of 84 mmHg and 75th percentile AaDO2 of 23 mmHg). Twenty-six subjects (20%) showed severe desaturation (nadir SpO2 <90%) during the 6MWT, and 16 subjects (12%) showed severe hypoxemia (PaO2 <60 mmHg) at peak...
exercise during CPET. Peak AaDO2 and ∆SpO2-6MWT were increased in 49% and 27% of cases, respectively.

**Correlations**

∆SpO2-6MWT and peak AaDO2 were both significantly correlated with DLco with intermediate correlation coefficients (Figure 1). ∆SpO2-6MWT was also significantly correlated with peak AaDO2 with a moderate correlation coefficient (Figure 1).

**Inter-test agreement analysis**

To assess the concordance between DLco, ∆SpO2-6MWT, and peak AaDO2 as predictors of gas exchange impairment, the variables were expressed as “normal” versus “abnormal” according to previously established thresholds. Gas exchange indices were all normal in 35 subjects (27%) and all altered in 24 subjects (18%), giving an overall concordance of 45% (Table 2). In 46 cases (35%), ∆SpO2-6MWT and peak AaDO2 were discordant. Kappa coefficients between 0.21 and 0.42 confirmed modest inter-test reliability (Table 3).

**Predictive values**

We evaluated the ability of DLco to predict ∆SpO2-6MWT and peak AaDO2 and the ability of ∆SpO2-6MWT to predict peak AaDO2 using transformed binary variables. DLco was a poor predictor of ∆SpO2-6MWT (PPV 36% and NPV 88%) and of peak AaDO2 (PPV 66% and NPV 78%). Importantly, normal DLco was a good predictor of the absence of severe desaturation during the 6MWT and at peak exercise during CPET (NPV 94% and 100%).

---

**Table 1** Results of pulmonary function tests, blood gas analysis, and 6MWT

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All subjects (n=130)</th>
<th>Stage I (n=11)</th>
<th>Stage II (n=69)</th>
<th>Stage III (n=11)</th>
<th>Stage IV (n=39)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance (m)</td>
<td>450 [100]</td>
<td>460 [110]</td>
<td>450 [100]</td>
<td>490 [100]</td>
<td>460 [125]</td>
<td>0.644</td>
</tr>
</tbody>
</table>

Data are presented as the median and [interquartile range]. a, P<0.05 between stages I and IV; b, P<0.05 between stages II and IV; c, P<0.05 between stages III and IV; d, P<0.05 between stages II and III. 6MWT, 6-minute walk test; ∆SpO2, oxygen desaturation [(resting – nadir) SpO2]; AaDO2, alveolar-to-arterial oxygen pressure difference; DLco, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; PaO2, partial pressure of oxygen; pred, predicted; TLC, total lung capacity; VO2 peak, peak oxygen uptake.
respectively). In contrast, decreased DLco did not predict severe desaturation during the 6MWT or at peak exercise during CPET (PPV 27% and 19%, respectively). \( \Delta \text{SpO}_2 \)-6MWT predicted peak AaDO\(_2\) with low NPV (60%) and PPV (74%) (Tables 4, 5). ROC curve analyses did not identify more relevant thresholds than those previously defined (Figure 2).

### Discussion

In the present study of a large population of patients with sarcoidosis, we found that DLco, \( \Delta \text{SpO}_2 \)-6MWT, and peak AaDO\(_2\) showed discordant results. In more than 50% of cases, one parameter among DLco, \( \Delta \text{SpO}_2 \)-6MWT, and peak AaDO\(_2\) conflicted with another parameter. These results were corroborated by the low to intermediate correlation coefficients, low Kappa coefficients, and low predictive values. However, \( \Delta \text{SpO}_2 \)-6MWT and peak AaDO\(_2\) were consistent measures of gas exchange since they both correlated with DLco and correlated with each other. DLco was a poor predictor of exercise-induced gas exchange impairment evaluated by \( \Delta \text{SpO}_2 \)-6MWT or peak AaDO\(_2\).

### Study limitations

The main limitation of the study concerns the definition of significance for peak AaDO\(_2\) and \( \Delta \text{SpO}_2 \)-6MWT. We selected a threshold of 30 mmHg for peak AaDO\(_2\) based on international recommendations proposing a range of 30–35 mmHg (29) and on the average age of our study population (27). Although this choice might have overestimated the proportion of subjects with increased peak AaDO\(_2\), it is unlikely to have influenced the finding of discordance between gas exchange indices because only 14 subjects (11%) had a peak AaDO\(_2\) between 30 and 35 mmHg, and the distribution of these patients between disease groups was not significantly different (data not shown). For \( \Delta \text{SpO}_2 \)-6MWT, we chose a threshold desaturation of 4% based on published data (25).
This threshold cannot be implicated in the discrepancy between gas exchange indices because the ROC curves failed to identify a better threshold to predict peak AaDO₂.

**Physiological interpretation and implications for clinical practice**

There were no differences in the distance walked during the 6MWT among the stage I–IV groups. This is in accordance with a previous study reporting a lack of correlation between sarcoidosis stages and the exercise tolerance or 6MWT distance (26,30). We hypothesize that the main exercise-limiting factor in sarcoidosis is not the physiological response to exercise but the symptoms, especially fatigue; however, this remains to be tested.

**Normal DLco and impaired gas exchange during exercise**

Thirty percent of subjects with normal DLco showed impaired exercise-related gas exchange, as indicated by increased ∆SpO₂-6MWT and/or peak AaDO₂. In chronic respiratory diseases of moderate severity, gas exchange efficiency may be conserved at rest but become insufficient during exercise. Sarcoidosis patients fail to increase the carbon monoxide transfer coefficient during exercise (31) due to bronchiolar obstruction, increased alveolocapillary membrane thickness, and vascular involvement (32). This result confirms that exercise tests improve the detection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal DLco (n=50)</th>
<th>Decreased DLco (n=80)</th>
<th>Normal ∆SpO₂-6MWT (n=95)</th>
<th>Increased ∆SpO₂-6MWT (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT-SpO₂ nadir &gt;90% (n=96)</td>
<td>44 (34%)</td>
<td>53 (41%)</td>
<td>93 (71%)</td>
<td>21 (16%)</td>
</tr>
<tr>
<td>6MWT-SpO₂ nadir &lt;90% (n=33)</td>
<td>6 (4%)</td>
<td>27 (21%)</td>
<td>6 (4%)</td>
<td>14 (11%)</td>
</tr>
</tbody>
</table>

Data are presented as the number of n=130 patients. 6MWT, 6-minute walk test; ∆SpO₂-6MWT, oxygen desaturation during the 6MWT; DLco, diffusing capacity of the lung for carbon monoxide.

![Figure 2](image-url) ROC curves. ROC curves determining the cut-off of DLco to predict ∆SpO₂-6MWT (left) and peak AaDO₂ (middle) and the cut-off of ∆SpO₂-6MWT to predict peak AaDO₂ (right). DLco, diffusing capacity of the lung for carbon monoxide; ∆SpO₂, oxygen desaturation [(resting – nadir) SpO₂]; 6MWT, 6-minute walk test; AaDO₂, alveolar-to-arterial oxygen pressure difference.
of gas exchange impairment in sarcoidosis, as previously reported for peak AaDO₂ (7). The present study shows that ∆SpO₂-6MWT is also a more sensitive index than DLco to assess gas exchange impairment in sarcoidosis. For clinical practice, gas exchange evaluation during the 6MWT and CPET might be helpful to understand symptoms unexplained by resting exams and to appreciate better the disease severity.

**Discordance between exercise tests**

In this study, 30% of subjects showed normal ∆SpO₂-6MWT but increased peak AaDO₂. This could be related in part to the lower workload elicited by the 6MWT (28) and to the lower sensitivity of SpO₂ compared with PaO₂ changes. Conversely, the 6MWT could reveal exercise-induced gas exchange impairment in patients with normal peak AaDO₂, which might be particularly helpful in the case of patients with unexplained symptoms and normal peak AaDO₂. Such discordance between exercise tests has previously been reported in idiopathic pulmonary fibrosis (33) and chronic obstructive pulmonary disease (34), but not in sarcoidosis. This could be related to the tests employed, since alveolar ventilation is lower and anaerobic metabolism is delayed during walking compared with cycling (35,36). Finally, the 6MWT and CPET provide complementary information on gas exchange adjustment during exercise. Interestingly, 17% of our patients presented with decreased DLco but normal ∆SpO₂-6MWT and peak AaDO₂. On explanation may be that normalization of gas exchange during exercise in sarcoidosis patients most likely results from improvement of ventilation/perfusion mismatch, although this has not been extensively investigated. Indeed, exercise may preferentially recruit the healthiest zones of the lung during exercise, as they are more compliant than inflamed areas.

**Conclusions**

In the present study, DLco, ∆SpO₂-6MWT, and peak AaDO₂ were independent measures of gas exchange in a large population of sarcoidosis patients. Neither ∆SpO₂-6MWT nor DLco was a good predictor of increased peak AaDO₂. In contrast, the main implication for clinical practice is that normal DLco is a good predictor of the absence of severe gas exchange impairment. ∆SpO₂-6MWT could represent a new index that provides distinct information of relevance for sarcoidosis evaluation and management, but this needs to be investigated by prospective and longitudinal studies.

**Acknowledgements**

The authors wish to thank Anne M. O’Rourke for editing the manuscript.

**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors disclose professional relationships with companies or manufacturers that will benefit from the results of the present study.

Ethical Statement: The study was approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine (No. CEPRO 2011-039) and written informed consent was obtained from all patients.

**References**

7. Marcellis RG, Lenssen AF, de Vries GJ, et al. Is there an added value of cardiopulmonary exercise testing in

2012;2012:657180.