Original Article

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]

[1]Department of Respiratory Medicine, Rare Disease Center, [2]Department of Biostatistics, [3]Lung 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 ($AaDO_2$) 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 (ΔSpO_2-6MWT) can be measured repeatedly, but its value in sarcoidosis is unknown. Here, we evaluated the ability of ΔSpO_2-6MWT 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, ΔSpO_2-6MWT, and peak $AaDO_2$ using correlation tests, inter-test reliability analyses, and predictive values. For the analyses of inter-test reliability and predictive values, DLco, peak $AaDO_2$, and ΔSpO_2-6MWT were considered as binary variables (normal/abnormal) according to previously defined thresholds.

Results: Correlation coefficients between DLco, ΔSpO_2-6MWT, and peak $AaDO_2$ 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 $AaDO_2$ with a positive predictive value (PPV) of 66% and a negative predictive value (NPV) of 78% and (II) increased ΔSpO_2-6MWT 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). ΔSpO_2-6MWT predicted peak $AaDO_2$ increase with a PPV of 74% and an NPV of 60%.

Conclusions: In a large population of sarcoidosis patients, neither ΔSpO_2-6MWT nor DLco was a good predictor of increased peak $AaDO_2$. 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 (ΔSpO_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, ΔSpO_2 during a 6MWT (ΔSpO_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 ΔSpO_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 ΔSpO_2-6MWT and peak $AaDO_2$ and, in particular, the ability of ΔSpO_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, ΔSpO_2-6MWT and peak $AaDO_2$, using correlation and inter-test agreement tests and evaluated the ability of ΔSpO_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, ΔSpO_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®). Single-breath DLco was measured. The DLco value was adjusted for hemoglobin by applying Cotes' equation: adjusted DLco = [DLco × (10.2 + hemoglobin)/(1.7 × 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® N-65). ΔSpO_2-6MWT was defined as the difference between the resting and nadir SpO_2. A desaturation ≥4% was considered significant (25).

CPET

CPET was performed to investigate dyspnea in 85 patients

(66%) and other symptoms, including fatigue and exercise intolerance, in 45 patients (34%). Subjects completed a triangular exercise test on an ergometric bicycle (Ergoline-Ergometrics 800®) using a standardized protocol, as detailed previously (26). Expired gases were extracted from each respiratory cycle with an Ergocard®. Heart rate and SpO_2 were monitored continuously using a 12-lead electrocardiogram and a pulse oximeter (Nellcor N-395), respectively. Arterial blood sampling was performed on room air at rest and at peak exercise. $AaDO_2$ was calculated from PAO_2, the 'ideal' compartment alveolar PO_2 determined from the alveolar gas equation [$PAO_2 = PiO_2 - (PaCO_2/RER)$] and PaO_2. Based on the age of the population, peak $AaDO_2$ above 30 mmHg was considered increased (27).

Statistics

Statistical analyses were performed using SPSS software (IBM SPSS Statistics 21). Normality of data distribution was assessed using the Shapiro-Wilk test. Quantitative data are presented as the median and interquartile range indicated in brackets. Qualitative data are presented as frequencies and percentages. Dependent variables (results of pulmonary function tests, blood gas measures, and 6MWT) were compared between disease stages using one-way ANOVA when data were normally distributed in all groups and using the Kruskal-Wallis test when at least one dataset was not normally distributed. Post hoc pairwise comparisons were performed using significance levels adjusted for multiplicity. Correlations between the quantitative variables DLco, ΔSpO_2-6MWT, and peak $AaDO_2$ in the whole population were evaluated using a bivariate Pearson test. Inter-test reliability, predictive values, and ROC curves were derived using DLco, ΔSpO_2-6MWT, and peak $AaDO_2$ as binary qualitative variables (normal *vs.* abnormal) according to the thresholds stated above (DLco < LLN, ΔSpO_2-6MWT ≥4%, peak $AaDO_2$ >30 mmHg). Concordance between DLco, ΔSpO_2-6MWT, and peak $AaDO_2$ 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 SpO_2 <90% during the 6MWT and PaO_2 <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 $kg \cdot m^{-2}$. 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, $AaDO_2$ at rest and peak exercise, and 6MWT results are detailed in *Table 1*. In summary, the stage IV sarcoidosis group had lower FEV_1, FVC, FEV_1/FVC, DLco, peak oxygen uptake (VO_2 peak), and peak PaO_2 and higher $AaDO_2$ than the stage I, II, and III groups. There were no significant differences in these variables between stage I, II, and III groups. ΔSpO_2-6MWT 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 PaO_2 and $AaDO_2$ 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 PaO_2 of 84 mmHg and 75th percentile $AaDO_2$ of 23 mmHg). Twenty-six subjects (20%) showed severe desaturation (nadir SpO_2 <90%) during the 6MWT, and 16 subjects (12%) showed severe hypoxemia (PaO_2 <60 mmHg) at peak

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

Parameters	All subjects (n=130)	Stage I (n=11)	Stage II (n=69)	Stage III (n=11)	Stage IV (n=39)	Adjusted P
Pulmonary function tests						
FEV_1 (% pred)	80 [31]	97 [19]	83 [25]	90 [11]	66 [30]^{a,b,c}	0.00001
FVC (% pred)	92 [24]	98 [26]	96 [21]	102 [19]	79 [32]^{a,b,c}	0.001
TLC (% pred)	90 [19]	88 [14]	90 [21]	93 [29]	88 [24]	0.644
FEV_1/FVC (%)	75 [15]	80 [8]	75 [15]	79 [12]	71 [24]^{a,b,c}	0.011
DLco (% pred)	71 [25]	82 [18]	76 [23]	73 [17]	55 [23]^{a,b,c}	0.00001
Kco (% pred)	91 [25]	94 [21]	94 [22]	86 [12]	77 [34]^{a,b}	0.0004
Blood gases						
Resting PaO_2 (mmHg)	90 [12]	89 [9]	90 [14]	91 [3]	88 [13]	0.644
Resting $AaDO_2$ (mmHg)	16 [12]	11 [13]	16 [8]	14 [8]	23 [12]	0.15
VO_2 peak (mL/kg/min)	20.2 [9]	23 [9]	21.3 [8]	21.3 [11]	16.9 [6]^{a,b}	0.021
VO_2 peak (% pred)	69 [9]	74 [31]	74 [28]	70 [36]	59 [26]^{a,b,c}	0.042
Peak PaO_2 (mmHg)	84 [25]	97 [17]	87 [21]	94 [12]	69 [22]^{a,b,c}	0.011
Peak $AaDO_2$ (mmHg)	29 [19]	15 [23]	27 [13]	24 [15]	44 [23]^{a,b,c}	0.011
6MWT						
Distance (m)	450 [100]	460 [110]	450 [100]	490 [100]	460 [125]	0.644
Resting SpO_2 (%)	96 [1]	96 [2]	97 [1]	96 [1]	96 [3]	0.644
Nadir SpO_2 (%)	94 [6]	95 [4]	94 [3]	96 [3]	89 [12]^{a,b,c}	3×10^{-8}
ΔSpO_2-6MWT (%)	2 [4]	2 [2]	2 [3]	0 [2]^{d}	4 [9]^{b,c}	0.011

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; ΔSpO_2, oxygen desaturation [(resting – nadir) SpO_2]; $AaDO_2$, alveolar-to-arterial oxygen pressure difference; DLco, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; PaO_2, partial pressure of oxygen; pred, predicted; TLC, total lung capacity; VO_2 peak, peak oxygen uptake.

exercise during CPET. Peak $AaDO_2$ and ΔSpO_2-6MWT were increased in 49% and 27% of cases, respectively.

Correlations

ΔSpO_2-6MWT and peak $AaDO_2$ were both significantly correlated with DLco with intermediate correlation coefficients (*Figure 1*). ΔSpO_2-6MWT was also significantly correlated with peak $AaDO_2$ with a moderate correlation coefficient (*Figure 1*).

Inter-test agreement analysis

To assess the concordance between DLco, ΔSpO_2-6MWT, and peak $AaDO_2$ 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%), ΔSpO_2-6MWT and peak $AaDO_2$ 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 ΔSpO_2-6MWT and peak $AaDO_2$ and the ability of ΔSpO_2-6MWT to predict peak $AaDO_2$ using transformed binary variables. DLco was a poor predictor of ΔSpO_2-6MWT (PPV 36% and NPV 88%) and of peak $AaDO_2$ (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%,

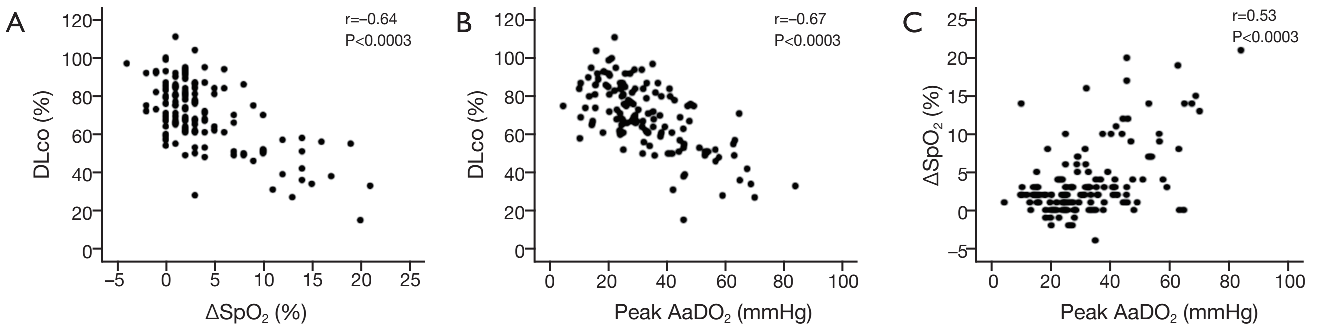

Figure 1 Correlations between DLco, ΔSpO_2-6MWT, and peak $AaDO_2$. DLco, diffusing capacity of the lung for carbon monoxide; ΔSpO_2, oxygen desaturation [(resting – nadir) SpO_2]; 6MWT, 6-minute walk test; $AaDO_2$, alveolar-to-arterial oxygen pressure difference.

Table 2 Distribution of gas exchange indices in sarcoidosis

Variable	Normal DLco (n=50)	Decreased DLco (n=80)
Normal ΔSpO2-6MWT (n=95)		
Normal peak $AaDO_2$ (n=57)	35	22
Increased peak $AaDO_2$ (n=38)	9	29
Increased ΔSpO_2-6MWT (n=35)		
Normal peak $AaDO_2$ (n=9)	4	5
Increased peak $AaDO_2$ (n=26)	2	24

Data are presented as the number (%) of n=130 patients. 6MWT, 6-minute walk test; ΔSpO_2-6MWT, oxygen desaturation during the 6MWT; $AaDO_2$, alveolar-to-arterial oxygen pressure difference; DLco, diffusing capacity of the lung for carbon monoxide.

Table 3 Kappa coefficients between gas exchange indices in sarcoidosis

Variable	Kappa coefficient	95% CI	P
DLco/ΔSpO_2-6MWT	0.21	0.08–0.33	0.002
DLco/peak $AaDO_2$	0.42	0.27–0.57	0.0003
ΔSpO_2-6MWT/peak $AaDO_2$	0.27	0.15–0.42	0.002

6MWT, 6-minute walk test; ΔSpO_2-6MWT, oxygen desaturation during the 6MWT; $AaDO_2$, alveolar-to-arterial oxygen pressure difference; DLco, diffusing capacity of the lung for carbon monoxide.

respectively). In contrast, decreased DLco did not predict severe desaturation during the 6MWT or at peak exercise during CPET (PPV 27% and 19%, respectively). ΔSpO_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, ΔSpO_2-6MWT, and peak $AaDO_2$ showed discordant results. In more than 50% of cases, one parameter among DLco, ΔSpO_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, ΔSpO_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 ΔSpO_2-6MWT or peak $AaDO_2$.

Study limitations

The main limitation of the study concerns the definition of significance for peak $AaDO_2$ and ΔSpO_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 ΔSpO_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 $AaDO_2$.

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.

Table 4 Predictors of severe exercise-induced gas exchange impairment in sarcoidosis according to DLco

Variable	Normal DLco (n=50)	Decreased DLco (n=80)
6MWT-SpO_2 nadir >90% (n=96)	44 (34%)	53 (41%)
6MWT-SpO_2 nadir <90% (n=33)	6 (4%)	27 (21%)

Data are presented as the number of n=130 patients. 6MWT, 6-minute walk test; ΔSpO_2-6MWT, oxygen desaturation during the 6MWT; DLco, diffusing capacity of the lung for carbon monoxide.

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 ΔSpO_2-6MWT and/or peak $AaDO_2$. 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 5 Predictors of severe exercise-induced gas exchange impairment in sarcoidosis according to DLco or ΔSpO_2-6MWT

Variable	Normal DLco (n=50)	Decreased DLco (n=80)	Normal ΔSpO_2-6MWT (n=95)	Increased ΔSpO_2-6MWT (n=35)
Peak PaO_2 >60 mmHg (n=114)	50 (38%)	64 (50%)	93 (71%)	21 (16%)
Peak PaO_2 <60 mmHg (n=16)	0 (0%)	16 (12%)	2 (1%)	14 (11%)

Data are presented as the number of n=130 patients. 6MWT, 6-minute walk test; ΔSpO_2-6MWT, oxygen desaturation during the 6MWT; DLco, diffusing capacity of the lung for carbon monoxide; PaO_2, partial pressure of oxygen desaturation.

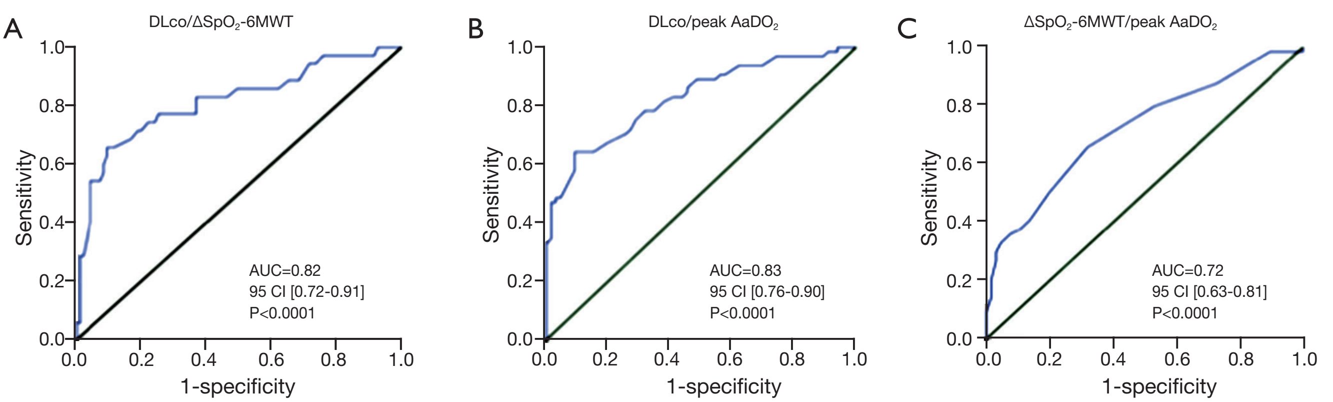

Figure 2 ROC curves. ROC curves determining the cut-off of DLco to predict ΔSpO_2-6MWT (left) and peak $AaDO_2$ (middle) and the cut-off of ΔSpO_2-6MWT to predict peak $AaDO_2$ (right). DLco, diffusing capacity of the lung for carbon monoxide; ΔSpO_2, oxygen desaturation [(resting – nadir) SpO_2]; 6MWT, 6-minute walk test; $AaDO_2$, alveolar-to-arterial oxygen pressure difference.

of gas exchange impairment in sarcoidosis, as previously reported for peak $AaDO_2$ (7). The present study shows that ΔSpO_2-6MWT 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 ΔSpO_2-6MWT but increased peak $AaDO_2$. This could be related in part to the lower workload elicited by the 6MWT (28) and to the lower sensitivity of SpO_2 compared with PaO_2 changes. Conversely, the 6MWT could reveal exercise-induced gas exchange impairment in patients with normal peak $AaDO_2$, which might be particularly helpful in the case of patients with unexplained symptoms and normal peak $AaDO_2$. 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 ΔSpO_2-6MWT and peak $AaDO_2$. 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, ΔSpO_2-6MWT, and peak $AaDO_2$ were independent measures of gas exchange in a large population of sarcoidosis patients. Neither ΔSpO_2-6MWT nor DLco was a good predictor of increased peak $AaDO_2$. In contrast, the main implication for clinical practice is that normal DLco is a good predictor of the absence of severe gas exchange impairment. ΔSpO_2-6MWT 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

1. Barros WG, Neder JA, Pereira CA, et al. Clinical, radiographic and functional predictors of pulmonary gas exchange impairment at moderate exercise in patients with sarcoidosis. Respiration 2004;71:367-73.
2. Drent M, De Vries J, Lenters M, et al. Sarcoidosis: assessment of disease severity using HRCT. Eur Radiol 2003;13:2462-71.
3. Lamberto C, Nunes H, Le Toumelin P, et al. Membrane and capillary blood components of diffusion capacity of the lung for carbon monoxide in pulmonary sarcoidosis: relation to exercise gas exchange. Chest 2004;125:2061-8.
4. Medinger AE, Khouri S, Rohatgi PK. Sarcoidosis: the value of exercise testing. Chest 2001;120:93-101.
5. Miller A, Brown LK, Sloane MF, et al. Cardiorespiratory responses to incremental exercise in sarcoidosis patients with normal spirometry. Chest 1995;107:323-9.
6. Kollert F, Geck B, Suchy R, et al. The impact of gas exchange measurement during exercise in pulmonary sarcoidosis. Respir Med 2011;105:122-9.
7. Marcellis RG, Lenssen AF, de Vries GJ, et al. Is there an added value of cardiopulmonary exercise testing in

sarcoidosis patients? Lung 2013;191:43-52.
8. Braam AW, de Haan SN, Vorselaars AD, et al. Influence of repeated maximal exercise testing on biomarkers and fatigue in sarcoidosis. Brain Behav Immun 2013;33:57-64.
9. 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 1999;160:736-55.
10. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
11. Baughman RP, Lower EE. Six-minute walk test in managing and monitoring sarcoidosis patients. Curr Opin Pulm Med 2007;13:439-44.
12. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428-46.
13. Wilsher M, Good N, Hopkins R, et al. The six-minute walk test using forehead oximetry is reliable in the assessment of scleroderma lung disease. Respirology 2012;17:647-52.
14. Manali ED, Lyberopoulos P, Triantafillidou C, et al. MRC chronic Dyspnea Scale: Relationships with cardiopulmonary exercise testing and 6-minute walk test in idiopathic pulmonary fibrosis patients: a prospective study. BMC Pulm Med 2010;10:32.
15. Chetta A, Aiello M, Foresi A, et al. Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:170-5.
16. Baldi BG, Araujo MS, Freitas CS, et al. Evaluation of the extent of pulmonary cysts and their association with functional variables and serum markers in lymphangioleiomyomatosis (LAM). Lung 2014;192:967-74.
17. Eaton T, Young P, Milne D, et al. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171:1150-7.
18. Hallstrand TS, Boitano LJ, Johnson WC, et al. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J 2005;25:96-103.
19. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:1084-90.
20. Standardized lung function testing. Official statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:1-100.
21. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J 1995;8:492-506.
22. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.
23. Kanber GJ, King FW, Eshchar YR, et al. The alveolar-arterial oxygen gradient in young and elderly men during air and oxygen breathing. Am Rev Respir Dis 1968;97:376-81.
24. Sorbini CA, Grassi V, Solinas E, et al. Arterial oxygen tension in relation to age in healthy subjects. Respiration 1968;25:3-13.
25. Prefaut C, Durand F, Mucci P, et al. Exercise-induced arterial hypoxaemia in athletes: a review. Sports Med 2000;30:47-61.
26. Wallaert B, Talleu C, Wemeau-Stervinou L, et al. Reduction of maximal oxygen uptake in sarcoidosis: relationship with disease severity. Respiration 2011;82:501-8.
27. Aguilaniu B, Maitre J, Diab S, et al. Detection of disturbances in pulmonary gas exchanges during exercise from arterialized earlobe PO2. Respir Physiol Neurobiol 2011;177:30-5.
28. Boros PW, Enright PL, Quanjer PH, et al. Impaired lung compliance and DL,CO but no restrictive ventilatory defect in sarcoidosis. Eur Respir J 2010;36:1315-22.
29. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:1451; author reply 1451.
30. Alhamad EH. The six-minute walk test in patients with pulmonary sarcoidosis. Ann Thorac Med 2009;4:60-4.
31. Young RC Jr, Fields HP, Scott JM, et al. Lung diffusing capacity response to exercise in sarcoidosis. A physiologic study. J Natl Med Assoc 1969;61:508-13.
32. Polychronopoulos VS, Prakash UB. Airway involvement in sarcoidosis. Chest 2009;136:1371-80.
33. Wallaert B, Wemeau-Stervinou L, Salleron J, et al. Do we need exercise tests to detect gas exchange impairment in fibrotic idiopathic interstitial pneumonias? Pulm Med

2012;2012:657180.
34. Poulain M, Durand F, Palomba B, et al. 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. Chest 2003;123:1401-7.
35. Cockcroft A, Beaumont A, Adams L, et al. Arterial oxygen desaturation during treadmill and bicycle exercise in patients with chronic obstructive airways disease. Clin Sci (Lond) 1985;68:327-32.
36. Mahler DA, Gifford AH, Waterman LA, et al. Mechanism of greater oxygen desaturation during walking compared with cycling in patients with COPD. Chest 2011;140:351-8.

Cite this article as: Chenivesse C, Boulanger S, Langlois C, Wemeau-Stervinou L, Perez T, Wallaert B. Oxygen desaturation during a 6-minute walk test as a predictor of maximal exercise-induced gas exchange abnormalities in sarcoidosis. J Thorac Dis 2016;8(8):1995-2003. doi: 10.21037/jtd.2016.06.39

