Reduction of Maximal Oxygen Uptake in Sarcoidosis: Relationship with Disease Severity

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Key Words

Sarcoidosis • Exercise • Dyspnea • Cardiopulmonary exercise testing • Pulmonary function

Abstract

Background: Patients with sarcoidosis frequently exhibit exertional dyspnea. Although the functional limitation might be related to ventilatory problems, some patients exhibited exertional dyspnea without significant abnormalities of pulmonary function tests (PFT). Therefore, the mechanisms responsible for exercise intolerance remain unclear. **Objectives:** The aim of this retrospective study was to determine the mechanisms responsible for exercise intolerance. **Methods:** Cardiopulmonary exercise testing (CPET) was performed in 157 dyspneic sarcoid patients (stage I: 29; stage II–III: 95; stage IV: 33) and VO_2 peak was correlated with radiological stage and resting PFT. **Results:** VO_2 peak was decreased in 73% patients, did not differ according to radiological stage and was correlated with VC, FVC, FEV_1 , TLC and DLCO. FVC was the major significant predictor of VO_2 peak explaining 17% of VO_2 variation. Among CPET variables, peak heart rate and VE/VO_2 at ventilatory threshold explained 22% of VO_2 alteration in stage I and stage II–III, and 9% in stage IV. In stage IV, V_D/V_T peak explained 41% of VO_2 altera-

tion. **Conclusion:** In conclusion, in the lower stages circulatory impairment and impaired heart rate response to exercise are involved in the exercise capacity limitation, whereas in stage IV the ventilatory and gas exchange impairment may be more important. CPET must be performed to accurately characterize the mechanisms responsible for exercise limitation and help the clinician in the management of the disease.

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Sarcoidosis is a systemic granulomatous disease of unknown etiology characterized by the formation of epithelioid cell granuloma without caseation. Chest involvement is frequent and usually the primary target organ [1]. Patients with sarcoidosis frequently exhibit exertional dyspnea and altered exercise tolerance. Several authors demonstrated the discrepancy between symptoms reported by the patients, (that is exertional dyspnea) and abnormalities of pulmonary function tests (PFT) in pulmonary sarcoidosis [2]. Dyspnea on exertion is frequently related to decreased lung capacity due to granuloma-

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tous pulmonary involvement and/or involvement of the diaphragm in some cases [3, 4]. However, although the functional limitation in some patients appears to be related to ventilatory problems, some patients exhibited exertional dyspnea without significant abnormalities of PFT [5–7].

Cardiopulmonary exercise testing (CPET) offers a sensitive evaluation of potential physiological disturbances in cardiovascular, respiratory, peripheral or neuromuscular responses to a standardized exercise [8–10]. However, exercise responses were rarely observed in sarcoid patients [2, 5, 11–15]. In the earlier ones, it has been showed that in these patients exercise intolerance was associated with a 25–30% reduction in maximal aerobic capacity compared to healthy age-matched controls [11, 12]. Latter, Miller et al. [13] reported that sarcoid patients with normal PFT and a normal diffusing capacity of the lung for carbon monoxide (DLCO) had abnormalities in ventilatory exercise response suggesting an occult state of lung impairment. Similarly, Karetzky and McDonough [14] confirmed the occurrence of a 30% decrease in maximal aerobic capacity in dyspneic patients with variable levels of DLCO in comparison with a healthy age-matched control group. Recently, Kollert et al. [6] reported in a series of 149 patients that 23% patients with normal spirometry had an impaired gas exchange during exercise but did not focus on maximal oxygen uptake and other CPET parameters. Lastly, Delobbe et al. [5] reported a similar reduced maximal exercise capacity associated with a low peak heart rate (HR) in sarcoid patients with a normal rest pulmonary function. Based on these findings we raised the hypothesis that reduction of maximal oxygen uptake was first not related to radiological stages of the disease and second mainly due to circulatory rather than ventilatory impairment. To establish this, we evaluated the physiological responses during a maximal CPET in dyspneic patients with sarcoidosis and their correlation with radiological stage of the disease.

Methods

A total of 157 Caucasian patients (75 females, 82 males) were consecutively referred for evaluation of dyspnea and CPET at the time of diagnosis or during follow-up, over a period of 6 years. A majority of patients (70%) were not treated at the time of investigation. Clinical data and results of CPET were retrospectively collected from two institutions at Calmette hospital in Lille and at Hylab, Clinique du Mail, in Grenoble. Only initial data were recorded when the patient was seen several times. Sarcoidosis diagnosis was confirmed by histopathological examination in all cases. Radiographic stages were defined in accordance with the ERS/

ATS 1999 statement on sarcoidosis [1] and classified as: stage I = bilateral hilar lymphadenopathy; stage II = bilateral hilar lymphadenopathy plus pulmonary infiltrations; stage III = pulmonary infiltrations without hilar lymphadenopathy; stage IV = evidence of pulmonary fibrosis with cicatricial changes [1].

Dyspnea during daily life activities was assessed at the time of evaluation with the modified MRC self-administered questionnaire consisting of 6 questions about perceived breathlessness from 0 (no dyspnea) to 5 (very severe dyspnea: too breathless to leave the house or breathless when dressing or undressing). Patients with MRC 0 were excluded of the study.

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), FEV₁ to FVC ratio, total lung capacity (TLC) and functional residual capacity (FRC) were measured by plethysmography with a Jaeger-Masterlab[®] cabin. DLCO (ml CO · min⁻¹ · mm Hg⁻¹), after adjusting for hemoglobin concentration in g · dl⁻¹, according to Cotes' equation: corrected (Hb) DLCO = DLCO (10.2 + Hb)/(1.7 × Hb). Predicted normal values were derived from standard equations [16, 17].

CPET was carried out using a standardized protocol [18]. Each patient underwent a symptom-limited incremental exercise test on an ergometric bicycle (Ergoline-Ergometrics 800[®]). The protocol included a warm-up period of 3 min at 20 W, a progressive increasing work rate in a ramp fashion and 3 min recovery. The work rate increment for each ramped exercise test was individualized [8] (range 8–30 watts · min⁻¹). During exercise, HR was monitored continually by 12-lead ECG and arterial oxygen saturation (SaO₂) was measured by pulse oximetry with a Nellcor N-395 apparatus. The expired gases were analyzed with an Ergocard[®]. We focused on oxygen consumption (VO₂), carbon dioxide production (VCO₂), minute ventilation (V_E) and tidal volume (V_T). The oxygen pulse (VO₂/HR) was calculated. Blood gas pressures and lactatemia were determined at rest and at maximal exercise. The ventilatory threshold was determined using the identification of the level of VO₂ at which the slopes of the V_E and VCO₂ curves begin to exceed that of the VO₂ curve. Ventilatory reserve was calculated as follows: ventilatory reserve = [predicted maximum minute ventilation (MMV) – peak V_E (V_E peak)]/MMV, with MMV estimated with the equation MMV = FEV₁ × 40. Peak HR (HR peak) was expressed as a percentage of maximum predicted heart rate, which was calculated as follows: HR max = 210 – 0.65 × age. The dead space (V_D/V_T) was calculated according to Bohr's equation corrected for the additional instrumental dead space: V_D/V_T = (PaCO₂ – PECO₂ mean)/PaCO₂ – [V_D (machine)/V_T], where PECO₂ is the partial pressure of expired CO₂. Predicted values for VO₂ max were calculated from reference equations [19]. Poor motivation was not a factor interfering with our analysis as suggested by the fact that all of the 157 patients had one or more of the following criteria: breathing reserve less than 15%, peak HR more than 90% of predicted, peak lactate more than 7 mEq/l, peak exercise PaO₂ less than 55 mm Hg or peak VE/VO₂ more than 35 [18, 20]. Approval for the use of these data was provided by our local ethical committee.

Statistical Analysis

The continuous variables were reported as means ± SD since the distributions were symmetric. Qualitative variables were given as frequency and percentage. One-way ANOVA was used to determine differences according to radiographic stage after checking the equality of variances with the Levene test. Post hoc analyses

Fig. 1. FVC, DLCO, peak VO_2 , peak HR, peak $\Delta\text{P(A-a)} \text{O}_2/\Delta\text{VO}_2$ and peak $\text{V}_\text{D}/\text{V}_\text{T}$ in sarcoid patients with stage I, stage II–III and stage IV. FVC, DLCO, peak VO_2 and HR are shown as percentage predicted values. $\Delta\text{P(A-a)} \text{O}_2/\Delta\text{VO}_2$ is expressed as mm Hg/l.

Table 1. Demographic characteristics of the 157 patients

Age, years ^a	47 ± 11 (24–74)
Sex ratio	1.08
BMI ^a	26.4 ± 6.7 (15.8–46.5)
Smokers ^b	20 (16)
Length of disease, years ^a	5.7 ± 6.4 (0–31)
Dyspnea MRC 1	43
Dyspnea MRC 2	41
Dyspnea MRC 3	16
Systemic oral steroids ^b	40 (25.4)
Inhaled steroids ^b	18 (11.4)
β-Blockers ^b	6 (4)

^a Results are expressed as means ± SD with ranges in parentheses. ^b Results are expressed as numbers of patients with percentages in parentheses.

were performed using Bonferroni correction. Correlations of VO_2 peak with the determinants were estimated with Pearson correlation coefficients. Variables which were significant with p value < 0.2 were introduced in a stepwise linear regression. A bootstrap validation on each final model was carried out to test their validities [21]. The predictive power of each model was assessed by the r^2 . Data were analyzed with SAS software version 9.1 (SAS, Chicago, Ill., USA). Statistical significance was considered at $p \leq 0.05$.

Results

Clinical Characteristics and Rest PFT

The mean age of the 157 patients was 46.7 ± 10.8 years (range 24–74) and time from diagnosis was 5.7 ± 6.4 years (range 3 months to 31 years). There were 29 (18.5%) patients in stage I, 80 (51%) patients in stage II, 15 (9.5%) patients in stage III of the disease and 33 cases (21%) were classified as stage IV. Because lung function indices were not statistically different between stage II and III, they were grouped for analysis. Most of the patients were moderately dyspneic during daily life activities (table 1). Twenty patients were smokers (24 pack-years) and 12 were ex-smokers (6 pack-years).

As expected, resting PFT values were significantly more altered in stage IV than in stage I and II–III (table 2).

Exercise Responses

A maximal symptom-limited exercise was obtained in all cases judged on symptoms and/or a functional limitation as defined in methods. Leg fatigue alone was the main cause (46%) of exercise intolerance, whilst dyspnea was noted alone or in combination with leg fatigue in 34

Table 2. Pulmonary function tests in 157 patients with sarcoidosis classified according to radiological stage of the disease

	All (n = 157)	Stage I (n = 29)	Stage II–III (n = 95)	Stage IV (n = 33)	p value I vs. II–III	p value I vs. IV	p value II–III vs. IV
Age, years	47 ± 11	44 ± 11	46.6 ± 11	49.4 ± 8	0.80	0.36	0.65
BMI	26.4 ± 6.7	26.3 ± 5	26.4 ± 5	26.5 ± 8.7	1	1	1
FVC ^a	91.4 ± 20	100 ± 18	92 ± 18	81 ± 22	0.12	0.0003	0.01
FEV ₁ ^a	84.1 ± 21	96 ± 18	86 ± 19	69 ± 21	0.06	<0.0001	<0.0001
FEV ₁ /FVC	88.4 ± 13.7	92 ± 9	90 ± 12	80 ± 17	1	0.001	0.0009
RV ^a	95.4 ± 30	95 ± 33	93 ± 33	97 ± 25	0.28	0.15	1
FRC ^a	90.9 ± 21	90 ± 23	91 ± 23	92 ± 18	0.29	0.22	1
TLC ^a	91.8 ± 15.5	97 ± 16	91 ± 15	89 ± 16	0.30	0.17	1
DLCO ^a	74.6 ± 19.5	82 ± 13	76 ± 19	63 ± 21	0.59	0.001	0.003
pH	7.43 ± 0.03	7.43 ± 0.04	7.43 ± 0.03	7.43 ± 0.03	1	1	1
PaO ₂ , mm Hg	89.6 ± 10.2	94.1 ± 8.6	88.9 ± 10	85.6 ± 17	0.0529	0.03	1
PaCO ₂ , mm Hg	36.6 ± 3.9	35.8 ± 4	36.6 ± 3.9	37 ± 3.7	0.89	0.619	1
P(A-a)O ₂ , mm Hg	17.9 ± 9.3	14.2 ± 7.7	18.1 ± 8.9	20.5 ± 10.8	0.134	0.021	0.57

^a Results expressed as percentages of predicted values.

and 14%, respectively. The remaining patients stopped because of general fatigue.

Only 27% of sarcoid patients exhibited normal CPET. As shown in table 3, 114 of the 157 patients (73%) had low VO₂ peak (<84% predicted values). The value of VO₂ peak, expressed as percent predicted value, was identical between the 3 radiologic or MRC (dyspnea during daily life activities) groups.

Ventilatory (V_E max, V_T/FVC max, breathing frequency, V_E/O₂ and V_E/VCO₂ at ventilatory threshold and at peak exercise) and cardiocirculatory responses (HR peak, O₂ pulse, ΔVO₂/ΔW and ΔHR/ΔVO₂) were similar among the 3 groups. As expected from resting PFT, ventilatory reserve was lower in stage IV. A significant progressive impairment in pulmonary gas exchange was observed along the stage severity with an increase in P(A-a)O₂, V_D/V_T and PaCO₂ and a decrease in PaO₂. Indeed peak P(A-a)O₂ and peak V_D/V_T were significantly higher in stage IV (fig. 1), and a decrease in PaO₂ during exercise was only seen in stage IV. Similar results were found when treated patients were excluded from analysis. Eighteen patients (11%) demonstrated electrocardiographic abnormalities during exercise [13 arrhythmias (extrasystoles), 4 conduction disturbances and one disturbance of repolarization], which did not lead to stop exercise.

Finally, exercise responses did not significantly differ according to the cause of exercise limitation or level of dyspnea.

Predictors of VO₂ Peak

Significant correlations (p < 0.0001) between VO₂ peak and resting PFT [FVC, FEV₁, TLC, DLCO and P(A-a)O₂] were observed. Among the variables having a p value less than 0.2 in the univariate analysis (table 4), many were highly correlated which had led to multicollinearity in the multivariate regression. The following independent variables were thus selected by the expert: FVC, DLCO, SaO₂ (%), P(A-a)O₂ (mm Hg), and pH. In multivariate regression, FVC and P(A-a)O₂ (mm Hg) were statistically significant predictors of VO₂ max (p < 0.001 and p = 0.048, respectively). However, the resulting r² indicated that these 2 variables explained only 19% of the VO₂ peak [17% for FVC and 2% for P(A-a)O₂ (mm Hg)]. A stratified analysis by group showed that these 2 variables explained 16% of the VO₂ peak variation in stage I, 15% in stage II–III and 34% in stage IV, but only FVC was statistically significant.

Functional Parameters during CPET and VO₂ Peak Variation

Significant correlations between peak VO₂ and quantifiable parameters of CPET [V_E/VO₂ (p < 0.0001), V_E/VCO₂ (p = 0.006), peak HR (p < 0.0001), peak oxygen pulse (p < 0.0001), ΔHR/ΔVO₂ (p = 0.018), peak pH (p = 0.004), peak SaO₂ (p = 0.017), peak lactatemia (p = 0.0001), peak P(A-a)O₂ (p = 0.017), ΔP(A-a)O₂/ΔVO₂ (p = 0.018) and V_D/V_T peak (p = 0.003)] were observed. Among the variables having a p value less than 0.2 in the univariate analysis (table 5), many were highly correlated which led

Table 3. Cardiopulmonary exercise test results in 157 patients with sarcoidosis classified according to radiological stage of the disease

Maximal exercise data	All patients (n = 157)	Stage I (n = 29)	Stage II–III (n = 95)	Stage IV (n = 33)	p value I vs. II–III	p value I vs. IV	p value II–III vs. IV
Workload ^a	78 ± 26	71 ± 18.1	81 ± 26	75 ± 23	0.34	1	0.20
Workload, W	114 ± 42	106 ± 37	119 ± 41	105 ± 38	0.36	1	0.22
VO ₂ , %pred	73.4 ± 18	72 ± 17.2	76 ± 17	68 ± 21	0.58	1	0.39
VO ₂ peak, ml/kg/min	21.5 ± 7	20.5 ± 6	22.2 ± 6.2	20.1 ± 8.43	0.36	1	0.16
ΔVO ₂ /ΔW, ml/W	11.4 ± 3	11.2 ± 3	12.2 ± 5	11 ± 3.5	1	1	0.85
V _E , l/min	64.7 ± 19.2	59.1 ± 14	66.7 ± 21	61.2 ± 16.8	0.07	1	0.1287
V _E /VO ₂ , VT	36.7 ± 7.6	35.7 ± 8.7	36.5 ± 7.7	38 ± 6	1	0.64	0.86
V _E /VCO ₂ , VT	40.2 ± 7	38.7 ± 7	40.4 ± 7.6	40.8 ± 6.7	0.84	0.80	1
BF max, min ⁻¹	38.6 ± 11	35.4 ± 10	38.8 ± 10	41 ± 10.4	0.36	0.14	1
Ventilatory reserve, peak ^a	27.6 ± 21	40 ± 15	26 ± 21	20 ± 19	0.003	0.0004	0.46
V _T peak, %FVC	49.2 ± 9	47 ± 10.4	49.4 ± 9	50.6 ± 9.3	0.65	0.38	1
HR peak ^a	85.9 ± 9.9	85.8 ± 11.3	86.3 ± 9.8	85 ± 8.8	1	1	1
Oxygen pulse peak ^a	83 ± 22.7	83.8 ± 17	85.3 ± 20	75.6 ± 30	1	0.47	0.11
ΔHR/ΔVO ₂	60 ± 27	64.9 ± 28	55 ± 23	68.8 ± 33	0.30	1	0.04
Lactatemia peak, mmol/l	7.3 ± 2.9	7.8 ± 3.3	7.3 ± 2.8	7.2 ± 2.7	1	0.71	1
pH peak	7.38 ± 0.04	7.39 ± 0.05	7.38 ± 0.04	7.37 ± 0.04	1	1	1
PaO ₂ peak, mm Hg	86.6 ± 16.2	99.2 ± 9.7	87.2 ± 15.1	74.6 ± 15.4	0.0005	<0.0001	<0.0001
PaCO ₂ peak, mm Hg	34.9 ± 5.1	33.7 ± 5.5	34.5 ± 4.8	37.1 ± 5	1	0.03	0.03
ΔP(A-a)O ₂ /ΔVO ₂ , mm Hg/l	14.1 ± 13.4	6.8 ± 9.3	12.4 ± 10	24 ± 19	0.29	<0.0001	<0.0001
P(A-a)O ₂ peak, mm Hg	31.2 ± 13.8	20 ± 8	31 ± 12	41 ± 14	0.0003	<0.0001	0.0003
V _D /V _T peak	0.27 ± 0.1	0.21 ± 0.09	0.27 ± 0.09	0.33 ± 0.09	0.025	<0.0001	0.0024

VT = Ventilatory threshold. ^a Results are expressed as percentages of predicted values.

Table 4. Correlation of clinical and functional variables at rest with VO₂ peak in 157 patients with sarcoidosis

	Correlation (r)	p value
Age	-0.077	0.344
BMI	-0.098	0.226
Length of disease	-0.112	0.166
TLC ^a	0.287	0.001
FVC ^a	0.416	<0.0001
FEV ₁ ^a	0.372	<0.0001
FEV ₁ /VC	0.127	0.117
DLCO ^a	0.285	0.001
DLCO/VA ^a	0.05	0.542
SaO ₂ , %	0.124	0.127
P(A-a)O ₂ , mm Hg	-0.238	0.003
pH	-0.12	0.137

^a Results expressed as percentage of predicted values.

Table 5. Correlation of variables obtained during clinical exercise testing with VO₂ peak in 157 patients with sarcoidosis

	Correlation (r)	p value
V _E /VO ₂ at VT	-0.315	<0.0001
V _E /VO ₂ peak	-0.243	0.003
V _E /VCO ₂ at VT	-0.223	0.006
V _E /VCO ₂ peak	-0.215	0.007
HR peak	0.322	<0.0001
VO ₂ /HR peak	0.763	<0.0001
ΔHR/ΔVO ₂	-0.19	0.018
pH peak	-0.281	0.0004
Lactatemia peak	0.316	0.0001
P(A-a)O ₂ peak	-0.194	0.017
ΔP(A-a)O ₂ /ΔVO ₂	-0.19	0.018
V _D /V _T peak	-0.241	0.003

VT = Ventilatory threshold.

to multicollinearity in the multivariate regression. The following independent variables were thus selected by the expert: $\text{VE}/\text{VO}_2 V_T$, peak VE/VO_2 , peak HR VO_2/HR , $\Delta\text{HR}/\Delta\text{VO}_2$, peak pH, peak lactatemia, peak $\text{P(A-a)}\text{O}_2$, $\Delta\text{P(A-a)}\text{O}_2/\Delta\text{VO}_2$ and peak V_D/V_T . In multivariate regression, HR peak and $\text{VE}/\text{VO}_2 V_T$ were statistically significant predictors of VO_2 peak. The resulting r^2 indicated that these 2 variables explained 22% of the VO_2 peak variation (16% for HR peak and 6% for $\text{VE}/\text{VO}_2 V_T$). A stratified analysis by the radiological stage showed that these 2 variables explained 22% of the VO_2 peak variation in stage I, 22% in stage II–III and 9% in stage IV. A specific analysis for stage IV showed that V_D/V_T max explained 41% of VO_2 peak variation.

Discussion

In this study, which was conducted in a large population of dyspneic patients with sarcoidosis, we found a high prevalence of abnormal exercise responses, suggesting the presence of gas exchange abnormalities, abnormal cardiovascular and ventilatory function impairment and muscle fatigue. These heterogeneous abnormalities led to a decreased exercise capacity in three fourths of the patients. There were three major findings: first, in this large group of sarcoid patients exhibiting dyspnea upon effort, a 25% reduction in VO_2 peak was observed; second, VO_2 peak was decreased in a similar importance in the three groups of patients, whatever the radiological stage and severity of the disease; third, physiologic defects accounting for the reduced peak VO_2 in our patients with sarcoidosis were more likely circulatory than ventilatory, with accompanying gas exchange impairment in advanced radiological stages.

Pulmonary diseases can result in multiple abnormalities of both gas exchange and cardiovascular or ventilatory responses to exercise. Patients exhibited a 25% lower maximal workload and/or VO_2 peak than control predicted values. Our results are in agreement with previous studies demonstrating such a reduction of VO_2 peak in sarcoidosis [5, 13, 14, 20, 22, 23]: 27% decrease according to Sietsema et al. [22] and 26% according to Delobbe et al. [5]. Interestingly, our results are in agreement with Karetzky and McDonough [14], who reported similar values of VO_2 peak (21 vs. 21.5 ml/min/kg in our study).

Exercise capacity is impaired in a similar proportion whatever the radiographic stage. Our study is the largest series reporting results according to radiological stage in sarcoidosis [2, 24–26]. Medinger et al. [24] reported sim-

ilar results in stage 1, 2 and 4 (80, 73 and 66% of VO_2 peak predicted values, respectively). Athos et al. [25] demonstrated a decreased VO_2 peak in more than 50% out of 39 patients with stage II and III. Barros et al. [26] reported that VO_2 reduction was similar whatever the radiological stage. However these studies were performed in a limited number of patients.

Conflicting results coexist in the literature demonstrating either the lack of correlation between PFT and VO_2 peak according to the radiological stage [2] or a good correlation between VO_2 peak and FVC [14] or DLCO [22]. However, these studies had a limited number of patients. Our study demonstrated that only FVC is a significant predictor of VO_2 peak but explained only 17% of VO_2 alteration.

Our results suggest that physiologic defects accounting for the reduced VO_2 peak were both circulatory and ventilatory. Indeed, in stages I and II–III, reduced exercise capacity is not associated with significant ventilatory or gas exchange abnormalities, and patients did not exhibit ventilatory limitation as reflected by ventilatory reserve at maximal exercise, which was not decreased indicating additional ventilatory possibilities. Two factors were found to explain in part VO_2 alteration: peak HR and $\text{VE}/\text{VO}_2 V_T$. Interestingly on one hand, peak HR was low at VO_2 peak; on the other hand, HR increment during exercise was abnormally high as demonstrated by a high $\Delta\text{HR}/\Delta\text{VO}_2$ and low VO_2/HR peak.

HR peak was low in a large proportion of patients. Our results are in agreement with previously published studies, and it is unlikely that low HR peak was related to a submaximal study, since according to Wasserman et al. [27] and Jones [9], all patients exhibited criteria of a maximal symptom-limited exercise. Indeed a reduced HR of a similar magnitude can also be noted in values reported by Karetzky and McDonough [14], although this point was not discussed by the authors. Delobbe et al. [5] demonstrated in patients with normal resting PFT a lower HR response to exercise in sarcoidosis, which may account at least in part for the observed maximal exercise limitation. In our study, HR peak was similar between the 3 groups and was found to explain 16% of VO_2 variation. It is likely that an impaired HR response to exercise may reflect circulatory impairment and cardiac involvement in the disease process [28] and have effects on limitation in exercise capacity in stages I and II–III sarcoid patients. The impaired HR response to exercise in sarcoidosis could be related to a sinus and/or atrioventricular conduction dysfunction secondary to myocardial conducting system infiltration particularly

vulnerable to sarcoid granulomas [29, 30]. Subclinical cardiac dysfunction in sarcoidosis secondary to granulomatous infiltration resulting in sinus node or resting ventricular dysfunctions have also previously been reported [28, 31, 32]. Lastly, histological examination of heart specimens from sarcoidosis patients indicate myocardial infiltration by noncaseating granulomata in up to 30% of cases [28, 33], involving both atrial and ventricular heart chambers.

The VO_2 to HR ratio, conventionally named the oxygen pulse, reflects the amount of O_2 extracted per heart beat. The O_2 pulse has been used by some as an estimate of stroke volume during exercise [9, 34]. A low value of O_2 pulse at peak exercise may be interpreted as resulting from a reduced stroke volume [9, 34, 35] and/or as a failure of skeletal muscle O_2 extraction [9]. The low values of oxygen pulse, which is independent of motivation, also support the hypothesis that exercise intolerance might be due to impaired O_2 transport (circulatory impairment). This finding has been previously observed by Hansen and Wasserman [20] in a series of 42 patients with various interstitial lung diseases. However, this hypothesis did not exclude the fact that low oxygen pulse might also be related to deconditioning, fatigue [36], steroid myopathy in some patients (but only 30% were treated at the time of the study) or muscle involvement [8, 37]. A recent paper also reported low values of oxygen pulse due to atrium compression by lymphadenopathies in sarcoidosis [38].

Our study also suggests that the extent of hyperventilation, as demonstrated by V_E/VO_2 , plays a role in VO_2 limitation. V_E/VO_2 is an expression of the ventilatory load of exercise. The use of V_E/VCO_2 to measure hyperventilation is much less satisfactory in that VCO_2 exhaled via the mouth increases as a function of V_E , which is not the case for V_E/VO_2 because V_E and VO_2 are independent [39]. Hyperventilation on exercise reflects a nonspecific response of the body, providing evidence of a dysfunction in one or several of the links in the respiratory chain, without necessarily indicating the mechanism involved. Ventilation during exercise is regulated by multiple factors. Indeed, hyperventilation involves mechanisms that are still largely unknown [40]. The increase in the ventilatory response may be due, in part, to inefficient gas exchange, as reflected by the alveoloarterial oxygen gradient and V_D/V_T ratio.

Conversely, stage IV sarcoid patients exhibited gas exchange impairments (especially V_D/V_T) and ventilatory limitation (as demonstrated by low ventilatory reserve). Multivariate analysis demonstrates that, in stages IV,

high values of V_D/V_T explain 41% of VO_2 alteration. An increase in V_D/V_T reflects an increased inefficiency of ventilation (high ventilation-perfusion mismatch). In an advanced stage of the disease, extensive scarring of the lung parenchyma and fibrosis may cause impairment of the diffusing capacity of the lungs, either by thickening of the alveolar wall or by reduction in the number of pulmonary capillaries that would lead to an increase in the size of the lung dead space. Increased physiological dead space in these patients might also be due to pulmonary hypertension, which is not rare in the course of sarcoidosis [41]. However, it was beyond the scope of the study to search for pulmonary hypertension in this large group of patients.

In conclusion, resting PFT proved to be poor predictors of exercise capacity: though maximum impairment of VO_2 was associated with greater decreases in TLC, FVC, FEV_1 and DLCO, FVC explained only 17% of VO_2 variation. Except in advanced radiological stages of the disease, ventilatory and gas exchange impairment are not responsible for exercise intolerance which is due, at least in part, to impaired HR response to exercise. Therefore, CPET appears to better determine mechanisms responsible for exercise intolerance in sarcoidosis and might prove useful to clinicians in the management of dyspnea related to sarcoidosis and decision of steroid treatment.

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