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Capacity of exercise in sarcoidosis: what is the importance of cardiopulmonary exercise test in these patients?

Dear Editor

Sarcoidosis is a heterogeneous multisystem granulomatous disease of unknown etiology [1]. Pulmonary involvement is frequent (90%). Diagnosis relies on three criteria: a) a compatible clinical and radiologic presentation; b) pathologic evidence of noncaseating granulomas; and c) exclusion of other diseases with similar findings, such as infections or malignancy [2]. The original staging of sarcoidosis has been developed from lung involvement as determined only by chest X-ray (CXR): stage 0 — normal cxr with proven extrapulmonary sarcoidosis; stage I — bilateral hilar lymphadenopathy without parenchymal disease; stage II — bihilar lymphadenopathy with parenchymal disease; stage III — parenchymal involvement without lymphadenopathy; stage IV — fibrosis [3]. Pulmonary function tests (at rest) and imaging methods are the most commonly used examinations and diagnostic tests in the follow-up and evaluation of the therapeutic response [4]. Dyspnea and exercise in sarcoidosis are often poorly correlated with resting lung function. Measurement of peak exercise capacity is likely to be helpful in assessing and monitoring the disease [5].

The authors performed a retrospective analysis of the files of 35 patients (13 men and 22 women) with pulmonary sarcoidosis who underwent an incremental cardiopulmonary exercise test (CPET) in a cycle ergometer at the Pulmonology Department of Coimbra Hospital and University Center from January 2008 to June 2018. The compromise of exercise capacity and the limiting factor during maximum CPET were evaluated, along with its relationship with the pulmonary function tests (PFT) and radiological stages of the disease.

The following changes in PFT were described: obstructive respiratory disorder [forced ventilatory volume in one second (FEV_1) / forced vital capacity (FVC) < 0.70], restrictive respiratory disorder [FVC < 80% predicted and total lung capacity (TLC) < 80% predicted] and reduced diffusion capacity of carbon monoxide ($T_{L,CO}$ < 80% predicted) [6].

CPET was interpreted according with suggested normal guidelines by the American Thoracic Society/American College of Chest Physicians [7] and ERS statement on standardisation of CPET in chronic lung diseases [8]. Criteria of normality for interpretation CPET are the following: $VO2_{max}$ or $VO2_{peak}$ > 84% predicted (normal exercise capacity); anaerobic threshold (AT) > 40% $VO2_{max}$ predicted (wide range of normal 40–80%); maximum heart rate (HRmax) > 90% age predicted; heart rate reserve (HRR) < 15 beats/min; blood pressure < 220/90 mm Hg; O_2 pulse > 80%; ventilatory reserve (VR): 72 ± 15% (wide normal range); respiratory frequency (FR) < 60 breaths/min; VE/VCO_2 (at AT) > 34; VD/VT < 0.3; pO_2 > 80 mm Hg; $P(A\text{-}a)O_2$ < 35 mm Hg.

The causes of exercise limitation in CPET found in this study were the following: alteration in gas exchange, due to desaturation (> 4% from baseline or decrease of 10 mm Hg from initial PO2), due ventilatory limitation translated by dynamic hyperinflation and due to cardiovascular limitation with frequent dysrhythmias during exercise. Physical deconditioning were defined by decreased $VO2_{max}$ or $VO2_{peak}$, reduced or normal VO2 at AT and decreased or normal peak HR.

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Table 1. Pulmonary function tests (PFT) results in 35 sarcoidosis patients and correlation between the results of PFT and cardiopulmonary exercise test (CPET)

Stage	PFT disorders	CPET alterations					
		Normal	Physical deconditioning	Hypertensive response	Gas exchange limitation	Ventilatory limitation	Cardiovascular limitation
I (7 patients)	Normal (7)	1	5	1			
II (13 patients)	Normal (5)		4	1			
	Restrictive + ↓ $T_{L,co}$ (1)				1		1
	Obstructive + ↓ $T_{L,co}$ (1)					1	
	Obstructive (1)						1
	↓ $T_{L,co}$ (5)	1	4				
III (9 patients)	Normal (6)		3	1		2	
	Obstructive (1)					1	
	Obstructive + ↓ $T_{L,co}$ (1)					1	
	↓ $T_{L,co}$ (1)		1		1		
IV (6 patients)	Normal (3)					1	1
	Restrictive (1)				1		
	Restrictive + ↓ $T_{L,co}$ (1)				1		
	↓ $T_{L,co}$ (1)		1				

$T_{L,co}$ — diffusing capacity for carbon monoxide

The mean age of the patients was 43.1 ± 12.5 years. Regarding smoking habits, 24 subjects (68.6%) were non-smokers and 11 (31.4%) smokers or ex-smokers. Twenty-three patients (65.7%) had complaints of dyspnea and the rest were asymptomatic. Seven persons (20.0%) were in stage I of the disease, 13 (37.1%) in stage II, 9 (25.7%) in stage III and 6 (17.1%) in stage IV. Twenty-one patients (60%) were on corticosteroid therapy or had already finished. As for the results of the functional respiratory study, 14 patients (40.0%) had changes (Table 1).

All performed maximum incremental CPET, limited by symptoms, on a cycle ergometer. Only 3 individuals (8.6%) stopped early due to a hypertensive response.

Exercise capacity was normal (% $VO2_{peak}$ > 84% predicted) in 2 patients (5.7%), 1 in stage I and the other in stage II. The remaining 33 patients (94.3%) had decreased exercise capacity. The average % $VO2_{peak}$ (predicted) in each stadium was as follows: I — 66.83 ± 9.83; II — 61.42 ± 8.41; III — 63.22 ± 16.70; IV — 65.83 ± 8.77 (without statistically significant difference, p = 0.57). The majority of patients (n = 31, 88.6%) reached the anaerobic threshold.

The causes of exercise limitation were the following: a) alteration in gas exchange in 4 (12.1%) patients; b) ventilatory limitation in 6 (18.2%) individuals; c) cardiovascular limitation in 3 (9.1%) patients. In the remaining cases, exercise was restricted by physical deconditioning.

The correlation between the results of PFT and CPET are shown in Table 1. In stage I (n = 7), all patients had normal PFT, however, only 1 person had normal CPET (% $VO2_{peak}$ 97% predicted).

In stage II (n = 13), 1 patient had no exercise limitation (% $VO2_{peak}$ 110% predicted). One person with restrictive disorder and decreased $T_{L,CO}$ had exercise limitations due to alterations in gas exchange and cardiovascular limitations. One patient with obstructive disorder and decreased $T_{L,CO}$ had limitations due to ventilatory changes with dynamic hyperinflation and 1 individual with obstructive disorder had cardiovascular changes during exertion.

In stage III (n = 9), 2 patients with normal PFT had exercise limitation due to ventilatory alteration with dynamic hyperinflation. Two patients with obstructive disorder (one also with decreased $T_{L,CO}$) had ventilatory changes in CPET.

In stage IV (n = 6), the 3 patients with normal PFT had exercise limitation (1 due to alterations in gas exchange, 1 due to ventilatory limitations and 1 due to cardiovascular changes). Two patients with restrictive disorder in PFT (one of them also with decreased $T_{L,CO}$) had limited gas exchange.

Thus, the results of this study showed the predominant role of CPET in the evaluation of patients with sarcoidosis, since it allowed to identify changes that were not noticeable in exams at rest. It allowed for a better understanding of the underlying pathophysiological changes and the most correct adjustments of therapies.

As an asset in the integration of clinical, imaging and respiratory function results, CPET is, however, an exam that is not systematically requested in patients with sarcoidosis, justifying the small number of our sample. In subjects with cardiovascular limitation without previous known cardiac changes, it was possible to raise the hypothesis of cardiac involvement by sarcoidosis, highlighting the need for a directed study.

Ultimately, it should be noted that in view of the clinical, imaging and functional dissociation, CPET allowed decisions to be made regarding therapy in patients with changes.

Conflict of interest

None declared.

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