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RESPIRATORY PATTERNS THROUGHOUT INCREMENTAL EXERCISE IN INDIVIDUALS WITH SARCOIDOSIS

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Abbreviations used: (PFT) pulmonary function test, (DLCO) diffusing capacity for carbon monoxide, (FEV1) forced expiratory volume in 1 s, (FVC) forced vital capacity, (FEV1/FVC) ratio of FEV1 to forced vital capacity,(COPD) chronic obstructive pulmonary disorder, (IC) inspiratory capacity, (VT) tidal volume, (IRV) inspiratory reserve volume, (VTmax) maximal tidal volume, (TLC) total lung capacity, (BTPS) body temperature and pressure saturated, (VE) minute ventilation, (RR) respiratory rate, (FRC) functional residual capacity, (SE) standard error, (VO2max) peak value of oxygen consumption, (VD/VT) dead space fraction

ABSTRACT

BACKGROUND: The signs and symptoms associated with Besnier-Boeck disease (sarcoidosis) lack uniformity. In the initial phase of sarcoidosis, individuals may have normal results on a pulmonary function test. The purpose of the research was to evaluate respiratory patterns during step-wise incremental exertion in individuals diagnosed with sarcoidosis who have unremarkable pulmonary function values and compare them with healthy controls.
METHODS: The study uses a retrospective design examining the exercise results of ten patients with the disease compared with nine healthy controls.
RESULTS: Neither the patients diagnosed with sarcoidosis nor the healthy controls had any evidence exhibited spirometrically in terms of airway restriction/obstruction. The results of incremental exercise revealed a lack of association between the IC values and the VTmax/IC upon completion of testing. There was a statistically significant difference in the VTmax as a percentage of IC upon completion of exercise (p-value 0.026) between the patients with the disease (90 +/- 6.3) and the healthy controls (72 +/- 3.4).
CONCLUSIONS: Breathing patterns are significantly different during exercise in individuals with sarcoidosis when compared to unaffected individuals, as evidenced when the VTmax is calculated as a percentage of IC. Breathing patterns can be utilized as a preliminary sign of sarcoidosis when pulmonary function tests are normal.

INTRODUCTION

Besnier-Boeck disease, more commonly known as sarcoidosis, is an inflammatory disease causing the formation of granulomas, the etiology of which is unknown. The disease is often diagnosed when patients are in their 20s or 30s. The disease can present in numerous ways; it sometimes manifests in a persistent form and sometimes has a spontaneous remission. Granulomas may affect lymph nodes and the lungs but may also be found in other organs, including the kidney, brain, heart, spleen, joints, eyes, skin and salivary glands. Patient outcomes are improved when the disease is detected and treated early.

Pulmonary sarcoidosis may present with cough and dyspnea. Exercise intolerance is also commonly seen in these patients. Symptoms may be attributed to musculoskeletal, cardiocirculatory, pulmonary-mechanical and gas exchange irregularities. [1-4]

Abnormalities in PFTs affect less than 1/3 of patients with confirmed sarcoidosis (stage 1 by radiography). There is a marked lack of consistency between the objectiveness of the PFT and the subjective symptoms experienced by patients with the disease. Frequently reported abnormalities include airway obstruction, abnormalities in gas exchange (i.e., reduced DLco) and restricted lung volume. Even when lung volume falls within normal ranges, measurement of DLco often shows diminished function of the lungs in patients with sarcoidosis. Other measurements that are often abnormal include FEV1 and a decreased ratio of FEV1 to FVC (FEV1/FVC). Therefore, there is no correlation between PFTs and the symptoms of the disease. [6-9]

Although patients with sarcoidosis frequently complain of exercise intolerance, static tests of pulmonary

functions are often unable to identify the factors that cause this condition. In fact, a recent study of 32 patients with sarcoidosis and dyspnea, exercise testing was required to accurately quantify their impairments.[10] In addition, a study by Lopes and colleagues showed that cardiopulmonary exercise testing (CPET) results were more effective than pulmonary functional test (PFT) measures at differentiating between patients with ground-glass opacity versus patients with traction bronchiectasis and honeycombing on high-resolution computed tomography (HRCT).[11] No statistical difference was observed between the patterns with abnormal CPET and patterns of abnormalities on HRCT ($p>0.05$). In fact, the reduced functional capacity of patients with traction bronchiectasis and honeycombing was detected by CPET. These studies suggest that there are obvious benefits to utilizing CPET to evaluate sarcoidosis patients.

In addition to the use of CPET for the determination of the mechanisms underlying exercise impairments in sarcoidosis patients. In a study of 157 dyspneic sarcoidosis patients with various radiologic disease stages, CPET revealed a link between impairments in circulation and heart rate responses to exercise and exercise capacity limitation in patients with lower disease stages; however, ventilatory and impairments in gas exchange played a major role in higher stage disease patients.[12] Similarly, in sarcoidosis patients with normal spirometry and decreased single-breath DLCO (n=9), 89% had excessive ventilation and 78% had increased dead space to tidal volume ratio, but only 5.8% had a widened alveolar-arterial oxygen pressure differences.[13] Therefore, in sarcoidosis patients with normal lung function CPET may highlight underlying pulmonary impairments. The best predictor of exercise limitations was decreased single-breast DLCO.

By contrast, the correlation between exercise tolerance and lung function at rest in COPD is well established. FEV1 is not a good predictor of a patient's tolerance for exercise. A comparison study of patients with COPD who had limitations in expiratory flow and subjects without COPD showed that measurements associated with dynamic over-inflation (i.e., IC) are less closely associated with FEV1 than tolerance of exercise. During exercise, healthy participants can increase VT but lose expiratory reserve and IRV; in participants who have COPD, VT can be increased only at expense of reduced expiratory and inspiratory reserve. In these patients, the maximum VT accomplished by exercise should be dependent upon the extent or degree of the IC. [22-24]

It may be beneficial to utilize CPET with blood gas analysis when clinical findings and physiological tests at rest are discordant. In patients with sarcoidosis, pulmonary gas exchange impairment (PGEI) at maximal exercise was exacerbated in patients with low DLco. According to Marcellis and colleagues, of the sarcoidosis patients that had a normal DLCO level at rest, 69.7% and 18.2% displayed a modest increase and excessive increase of P(A-a)O(2), respectively.[17] Sarcoidosis patients with normal resting PFT had significantly lower maximal workload and/or VO2max, maximal ventilation and tital volume relative to control patients. In contrast, dead space t tital volume ratio was higher in the sarcoidosis patients compared to the control patients. Although the peak exercise EKG was normal in most of the sarcoidosis patients, the heart rates for these patients were significantly lower than control patients (159±21.7 vs 182±13).[18] These data suggest that resting measurements do not accurately detect impaired exercise responses in sarcoidosis patients. This likely related to the inability of resting measurements to detect impairments in heart rate responses, which only become evident during exercise.

Ideally, it would be beneficial to have predictors of declining pulmonary function. A longitudinal study of 42 nonsmoking patients with thoracic sarcoidosis was designed to identify CPET measures that were predictive of patient outcomes.[19] At the initial evaluation and at the 5-year follow-up spirometry, DLCO and CPET were performed. Forced vital capacity (95.5% to 87.5%) and single-breath DLCO (93.5% to 84.5%) decreased significantly at the 5-year follow-up; and these findings were strongly correlated with P(A-a)O(2) and ΔSpO2 values ($p<0.0001$). P(A-a)O(2) and breathing reserve ≤40% were found to be independent variables that identified reduced pulmonary function. Therefore, initial exercise testing measurements can be used to identify patients with potentially poor prognosis, which can help clinicians improve the management of their disease.

Despite health-related quality of life being a major factor in patients with sarcoidosis, it is difficult to measure and to identify clinical markers that can predict health-related quality of life. Sarcoidosis patients (n=162) were administered the Sarcoidosis Health Questionnaire (SHQ) and Short Form-36 Survey (SF-36).[20] Multivariate regression analyses identified a composite model of distance-saturation product and Borg Dyspnea Scale score in the 6MWT that could better predict SF-36 scores ($R^2=0.33$) than SHQ ($R^2=0.24$). Therefore, these variables can be obtained using exercise testing, they are easy to capture in the clinic and can be monitored over time to measure the response to treatment regimens. The assessment of health-related quality of life and exercise pulmonary function provide the best insight into the prognosis and management of sarcoidosis.[21]

Therefore, it is logical to presume that, in the initial stages of sarcoidosis or in individuals or ethnic groups who are susceptible to the condition, lung impairment may be present that cannot be identified by static spirometric or pulmonary function tests. A recent study revealed gender and ethnic differences between 6-min walk distances (6MWD) for patients diagnosed with sarcoidosis.[22] In this study, we report on a retrospective research involving ten individuals with sarcoidosis who would normally be diagnosed as free of the disease according to standard PFTs. The goal was to determine and show early irregularities in function of the lungs during the performance of incremental exercise.

Methods

Participants

The authors reviewed the step-wise incremental exercise measurements of ten individuals with disease and contrasted their results with nine healthy controls. The design of the study involved the measurement of baseline PFTs, in addition to cycle ergometer symptom-limited maximal incremental exercise.

Pulmonary function tests

The subjects were examined while seated, during which spirometry was carried out utilizing an electronic spirometer which was calibrated. The volumes of the lung were established by plethysmography. Maximum voluntary ventilatory effort was calculated as described previously.

[23] The values recorded included: TLC, DLco, and FVC and FEV1 (in liters).

Exercise testing

A cycle ergometer (electrically braked) was used for the incremental symptom-limited exercise testing. Workloads of fifteen watts were increased in a stepwise fashion every two minutes. The participants wore a clip on their nose, were seated and breathed into a two-way valved mouthpiece with low resistance. Expired gases were evaluated a single breath at a time using a computerized system. Each signal was incorporated into the system's computer to calculate a 15 second moving average of VO2, RR, VT and VE. Gas measurements and air flow were altered to account for water vapor, ambient temperature and barometric pressure, expressed in BTPS units. The equipment used in the exercise testing was calibrated before each study using a 3 liter calibration syringe and gases of known concentrations. Widely utilized cutoffs for percent predicted allowed for categorization of resting functional variables. Predicted FRC and TLC differences were used for predicted values of IC. Arterial pressure, pulse and percent oxygen saturation were monitored continuously. The modified Borg scale (0 = no dyspnea to 10 = maximum dyspnea) was used to determine the level of dyspnea experienced by each participant. [24] The participants rated their amount of dyspnea after being taught the Borg scale.

Statistical Analysis

ANOVA (one-way) and Student's t test were utilized to measure differences between participants; 0.05 was established as the probability for type 1 error. Pulmonary exercise parameter mean values are recorded as mean +/- SE. As described previously, 95% CI (confidence interval) for the normal control subjects was established. The least squares method was used to determine the regression lines for exercise associations. [4]

Results

In order to perform comparative analysis, the data were computed as a percentage of predicted values (VO2max, FEV1, FVC, TLC and DLco) to make up for differences between individuals in terms of weight, height, age, sex, body mass index and other variables.

Results of spirometry testing measurements can be found in Table 1.

Table1. Comparison of pulmonary function tests between sarcoidosis and normal patients. All values are means ± SE.

Variables	Sarcoidosis	Control	(p value)
Age	43±4.8	47±4.5	(0.52)
FEV_1 %predicted	107±8.3	100±4.9	(0.51)
FVC %predicted	98±7.8	101±5.2	(0.73)
IC, liter	2.6±0.4	2.5±0.2	(0.38)
TLC, %predicted	106±6.6	111±3.1	(0.50)
DLCO predicted	97±5.4	87±2.5	(0.14)

The values for FVC and FEV1 for all of the subjects (ten sarcoidosis patients and the nine healthy subjects) were well within normal limits of the spirometric index and are expressed as % predicted.

In comparing the normal participants and the sarcoidosis participants, no significant differences were observed regarding the values of IC (in liters), DLco, % predicted and TLC.

Table 2 reveals the variables measured during exercise testing. The dead space (VD) to tidal volume (VT) ratio is higher (15 =+/- 2.8) in the sarcoidosis patients compared to the healthy patients (9.8 +/- 1.0). Although the p-value of 0.16 indicates that this difference is not statistically significant, it does indicate the presence of more dead space in sarcoidosis patients compared to controls.

Table2. R**esults of incremental exercise testing in sarcoidosis patients and normal subjects.**

Variables	Sarcoidosis	Control	(p value)
Age	43±4.8	47±4.5	(0.52)
VO2max %predicted	98±7.7	100±4.2	(0.80)
Heart rate max	167±9.8	162±6.0	(0.68)
VTmax liter	2.3±0.3	1.8±0.2	(0.20)
VT/IC %rest	32.8±3.7	23.8±1.8	(0.05)
VD/VTmax%	15±2.8	9.8±1.0	(0.16)

In the sarcoidosis (and a few normal) participants, high values for VO2max (approximately 5%) were discovered. The peak value VO2max was 98% in the sarcoidosis participants.

There was no relationship between IC and VTmax/IC following the exercise as shown by regression analysis (this data is not shown).

When shown as a percentage of the IC value, the VTmax for the sarcoidosis participants is (90 +/- 6.3). This value is (72 +/- 3.4) for the healthy controls; the difference between the groups was found to be significant (p= 0.026).

DISCUSSION

There is no "hard and fast" definition for diagnosis of sarcoidosis. Therapy is generally recommended for patients who present with lung infiltrates and decreased pulmonary function at rest, as well as an association of symptoms with these findings. Several studies have presented conflicting recommendations and reports; a few groups associate unusual incremental exercise responses with multiple abnormal PFTs and associated symptoms.[16]

While some groups have found that radiographic findings are a valid predictor of performance during exercise, the next best predictor is capacity for diffusion of CO.[25] The most frequent abnormality found in patients without clinically obvious disease was the determination of an increase in VD/VT (ratio of air taken in and air exhaled in a solitary breath to total capacity of the lung) during exercise.[26]

In the present study, the patients with sarcoidosis have normal capacity for diffusing CO2, as well as normal spirometry. Ventilation abnormalities, such as excessive VD/VT, are evidenced in the exercise testing as might be expected, although a higher tendency was observed for the sarcoidosis patients compared to the control group (15 +/- 2.8 versus 9.8 +/- 1.0).

This study is unique in that it specifically examines the relationship of VTmax to IC in patients with sarcoidosis. In normal patients, the VTmax can never exceed IC in rebreathing studies.[27] Only a portion of the IC is utilized during exercise in relation to VT. Accordingly, VTmax must be necessarily lower than the resting IC. A higher ratio of VTmax to IC predicts a decreased ability of the lung to keep air after expiration when compared to the total air volume.

In addition, exercise capacity in individuals with sarcoidosis may be confounded by other considerations, such as deconditioning and muscle weakness; hence VTmax is related closely to IC (resting) .[28]

Lastly, IC changes seem to relate more strongly to changes in patient perception of dyspnea, rather than other lung volume aspects. Earlier studies have reported a higher correlation of dyspnea with IC among volume and static flow measurements.[29-31]

CONCLUSION

This study is important as it demonstrates that the VTmax to IC ratio is a strong predictor of diminished lung

function as regards patients with sarcoidosis in the initial stages of the disease, even when other tests such as PFTs and exercise tests are deemed to be normal. This study is the first one to demonstrate this fact. Larger studies involving greater numbers of patients are needed in order to duplicate these findings. Potentially, this study can be used to identify sarcoidosis earlier in patients who have normal pulmonary function tests.

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