Six-minute walk test in sarcoidosis patients with cardiac involvement

Test 6-minutowego chodu u chorych na sarkoidozę płuc z zajęciem serca

The authors report no financial disclosure.

Abstract

Introduction: Cardiac involvement in sarcoidosis is of critical importance, due to the poor prognosis if this organ manifestation is left undiagnosed and untreated. The six-minute walk test (6 MWT) is a useful test to evaluate exercise tolerance of sarcoid patients. We aimed to assess the 6 MWT value in diagnosis, course and treatment monitoring of patients with cardiac sarcoidosis.

Material and methods: 47 patients were included: 22 with pulmonary sarcoidosis and cardiac involvement (13 women, 9 men), 25 with pulmonary sarcoidosis, with no changes in the heart (15 women, 10 men), and 18 healthy volunteers as controls (12 women, 6 men). Out of 22 patients with cardiac involvement 11 were treated for heart sarcoidosis with prednisone (9 pts — initial dose 60 mg daily and 2 pts — 40 mg daily). 11 pts in this group were not treated. In all patients sarcoidosis was confirmed histopathologically. Magnetic resonance imaging was used to diagnose involvement of the heart.

In the studied groups we assessed: heart rate (HR), oxygen saturation, distance in 6 MWT and Borg dyspnea score.

Results: Patients with cardiac sarcoidosis desaturated more during exercise (DSaO2max = 3.5 ± 3.2 vs. 0.38 ± 0.69; p = 0.004) and had a lower increase of HR in first minute during the 6 MWT (DHR1 = 21.81 ± 11.72 vs. 50.61 ± 12.35; p = 0.0001) when compared to healthy subjects. Significantly lower increase of HR in first minute of 6 MWT was observed in patients with cardiac sarcoidosis when compared to patients with pulmonary sarcoidosis with no cardiac involvement (DHR1 = 21.81 ± 11.72 vs. 38.8 ± 18.17, p = 0.01). After introduction of treatment in sarcoidosis group, significantly higher (p = 0.02) increase of HR in first minute of 6 MWT as compared to baseline test was observed.

Conclusions: The six-minute walk test is useful in diagnosing cardiac involvement in sarcoidosis. The increase in HR during exercise and decrease degree of desaturation were a good predictors of the response to therapy.

Key words: sarcoidosis (SA), cardiac sarcoidosis, six-minute walk test (6 MWT), magnetic resonance imaging (MRI)


Introduction

Sarcoidosis is a multi-organ disease of unknown aetiology. It occurs most commonly in people from 20 to 40 years of age, more frequently in women. The suspicion of sarcoidosis often arises from a routinely performed chest X-ray that shows enlarged hilar and mediastinal lymph nodes and/or disseminated interstitial pulmonary changes. Abnormal findings on imaging studies may be
accompanied by clinical symptoms (dry cough, low-grade temperature, increased sweating, impairment of exercise tolerance, erythema nodosum, pains and/or swelling of lower extremity joints). Many cases have an oligo- or asymptomatic course [1–5].

Lungs and/or intrathoracic lymph nodes are the most frequently affected organs. The use of computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) allows for better recognition of involvement of organs other than lungs [2–5]. According to the published data, skin sarcoidosis is present in 25% of cases [6], eyes are affected in 10–90% of cases (from 10–50% in Europe and United States up to 60–90% in Japan) [7, 8], liver in 50–80%, spleen in 10–50%, and lymph nodes in 30%. Involvement of the kidneys is rare [7, 9]. Sarcoidosis may also affect organs or organ systems essential for life. The involvement of the central nervous system (CNS) is estimated at around 10% [7] and symptomatic cardiac involvement at 2–10% of all patients suffering from sarcoidosis. However, autopsy studies show cardiac changes in 20–78% of cases [7, 10]. When modern imaging tools are applied to the investigation of extrapulmonary sarcoidosis, it appears that heart sarcoidosis is more frequent and may be present in as many as 40–60% of patients [11, 12].

The sarcoidosis of the heart may coexist with lung sarcoidosis, and it may be the only or the first symptom of sarcoidosis, but it can also persist after lung sarcoidosis remission. Magnetic resonance imaging with gadolinium is considered to be one of the most important tests in diagnosing cardiac involvement in the course of sarcoidosis [11, 12].

The diagnostic algorithm for cardiac sarcoidosis includes a resting ECG, a 24-hour ECG recording, an echocardiographic (echo) study, and a cardiac MRI [5, 11, 12].

We decided to assess the usefulness of the 6-minut walking test (6MWT) in the diagnostic process of cardiac sarcoidosis, as well as in the monitoring of the course of the disease and its response to the treatment.

**Materials and methods**

The studied group consisted of patients with various stages of pulmonary sarcoidosis and suspicion of cardiac involvement. All patients were hospitalised in the II Pulmonary Department of the National Institute of Tuberculosis and Lung Diseases in Warsaw, Poland. In all included patients sarcoidosis was confirmed by histopathological study, and the coexistence of the following conditions was excluded: pulmonary hypertension, anemia, musculoskeletal disorders, neurological disorders, and bronchial obstruction in spirometry. The cardiac involvement was recognised on the basis of gadolinium enhanced MRI (Signa Excite 1,5 T, GE, USA).

After having the MRI performed the patients were divided into two groups. One group consisted of patients with pulmonary sarcoidosis and cardiac involvement on MRI, the other group consisted of patients with pulmonary sarcoidosis without features of cardiac involvement on MRI study.

All patients with cardiac involvement were offered treatment with glucocorticosteroids (GCs). All of them were acquainted with detailed information on the treatment scheme and its potential adverse effects, on one hand, and with the danger of the untreated disease, on the other hand. Since not all of the patients with cardiac involvement agreed to the treatment, two subgroups within that group were identified: patients treated with GCs and patients without treatment.

The control group consisted of 18 healthy, non-obese volunteers with normal chest X-ray performed within the preceding 12 months.

All patients and all healthy volunteers had 6MWT. It was performed on a treadmill with continuous monitoring of oxygen saturation (transcutaneously), heart rate (HR), and walking speed. The distance covered during 6 minutes of walking was measured. Records of blood pressure were taken just before and after the exercise. The degree of the dyspnoea was assessed with help of the Borg scale.

The predicted values and lower limits of normal for 6MWT distance were calculated for each individual separately on the basis of Enright’s nomograms [13].

**Males**

\[
\text{Distance (predicted value)} = (7.57 \times \text{body height [cm]} - (5.02 \times \text{age} - (1.76 \times \text{body weight [kg]}) - 309 \text{ m} \\
\text{Lower limit of normal} = \text{predicted value} - 153 \text{ m}
\]

**Females**

\[
\text{Distance (predicted value)} = (2.11 \times \text{body height [cm]} - (5.78 \times \text{age} - (2.29 \times \text{body weight [kg]}) + 667 \text{ m} \\
\text{Lower limit of normal} = \text{predicted value} - 139 \text{ m}
\]

In patients with cardiac sarcoidosis treated with GCs the follow-up 6MWTs were performed 1, 3, 6, and 12 months after baseline assessment. The purpose of it was to follow up the changes in exercise capacity as well as to assess the treatment
results. The follow-up cardiac assessment included echo study at 1, 3 and 6 months of treatment and cardiac MRI after 12 months.

The study protocol was approved by the Ethics Committee of the National Institute of Tuberculosis and Lung Diseases.

Statistical Analyses

All statistical analyses were performed using Statistica 6.0 software. The results are presented as mean values and standard deviations. U Mann-Whitney test and ANOVA Kruskall-Wallis test were used for comparison between two groups and comparison between three or more groups, respectively. P < 0.05 was considered as statistically significant. For repeated measurements in patients with cardiac sarcoidosis treated with GCs Friedman’s ANOVA test was used. The multiple regression test was applied to identify the variables significant in determining the 6MWT distance.

Results

Forty-seven patients with pulmonary sarcoidosis and suspicion of cardiac sarcoidosis were included in the study (28 females – 59.57% and 19 males – 40.43%). Mean age was 47.65 ± 10.06 years. Stage I sarcoidosis was present in 8 patients (17.02%), stage II in 33 patients (70.21%), and stage III in 6 patients (12.76%). Mean follow-up time was 4.6 ± 6.65 years. In all patients the diagnosis of sarcoidosis was confirmed histopathologically: from bronchial mucous biopsy in 23 patients, from transbronchial lung biopsy in 17 patients, from video-assisted thoracoscopy in 2 patients, and from mediastinoscopy in 5 patients.

After the gadolinium enhanced cardiac MRI study results were obtained patients were divided into 2 groups. One group consisted of 22 patients with pulmonary sarcoidosis and MRI features of cardiac involvement. The other group consisted of 25 patients with pulmonary sarcoidosis, but without cardiac involvement according to the MRI result. Since some patients with cardiac sarcoidosis did not agree to treatment, 2 subgroups were distinguished among them: 11 patients treated with GC and 11 patients left without the treatment.

In 9 patients with cardiac sarcoidosis prednisolone in an initial dose of 60 mg per day and in 2 patients with an initial dose of 40 mg per day was commenced. The treatment was continued, with gradual reduction of the dose, for 2 years. The lower initial dose of prednisolone was used due to coexisting medical conditions (1 case) or the patient’s will (1 case).

The control group consisted of 18 healthy volunteers. The characteristics of the studied patients’ groups and the control group are shown in Table 1. A list of comorbidities and organs, other than lungs, affected by sarcoidosis is shown in Table 2.

**Table 1. Overall characteristics of the study groups (ANOVA and post hoc Tukey’s test)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cardiac sarcoidosis — with treatment n = 11</th>
<th>Cardiac sarcoidosis — no treatment n = 11</th>
<th>Pulmonary sarcoidosis with no cardiac involvement n = 25</th>
<th>Control group n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women/men)</td>
<td>8/3</td>
<td>5/6</td>
<td>15/10</td>
<td>12/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.9 ± 6.94*</td>
<td>43.36 ± 10.13</td>
<td>49 ± 10.96**</td>
<td>35.11 ± 13.09*/**</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>26.32 ± 3.09</td>
<td>27.66 ± 5.26</td>
<td>26.37 ± 4.47</td>
<td>25.45 ± 3.06</td>
</tr>
<tr>
<td>Stage of pulmonary sarcoidosis (n)</td>
<td>I°: n = 1</td>
<td>I°: n = 1</td>
<td>I°: n = 6</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>II°: n = 6</td>
<td>II°: n = 10</td>
<td>II°: n = 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III°: n = 4</td>
<td>III°: n = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The distance in 6 MWT [m]</td>
<td>514.81 ± 91.22*</td>
<td>567.09 ± 119.06</td>
<td>520.8 ± 96.22**</td>
<td>638.44 ± 53.96**/##</td>
</tr>
<tr>
<td>ΔHR1/ΔHR1</td>
<td>21.81 ± 11.72*</td>
<td>37.45 ± 16.5</td>
<td>38.8 ± 18.17†</td>
<td>50.61 ± 12.35††</td>
</tr>
<tr>
<td>Maximal desaturation (%)</td>
<td>3.5 ± 3.2§</td>
<td>1.9 ± 1.7</td>
<td>2.36 ± 2.87§§</td>
<td>0.38 ± 0.69§/§§</td>
</tr>
<tr>
<td>Speed [m/s]</td>
<td>4.52 ± 0.9</td>
<td>5.46 ± 1.27</td>
<td>4.71 ± 1.01</td>
<td>6.04 ± 0.62</td>
</tr>
</tbody>
</table>

* p = 0.008, ** p = 0.008, † p = 0.003, †† p = 0.0006, § p = 0.004, ‡ p = 0.04, ‘ p = 0.01, ‘‘ p = 0.0001, nd — not defined; BMI — body mass index; 6 MWT — six-minute walk test; ΔHR1 — increase of heart rate in 1. minute of test.
In baseline 6MWT mean distance was 520.8 ± 96.22 m in patients without cardiac involvement, 567.09 ± 119.06 m in patients with cardiac sarcoidosis that chose not to be treated, 514.81 ± 91.22 m in patients subsequently treated with GC, and 638.44 ± 53.96 m in healthy volunteers. The distance in the control group was significantly longer than in sarcoidosis patients (p = 0.0006), and than in patients with cardiac sarcoidosis who agreed to the treatment (p = 0.003) (Table 1). Among all sarcoidosis patients, only 5 (10%) covered a distance shorter than 400 m.

A negative correlation between patients’ age and the distance was found (R = −0.67; p< 0.001) (figure 1). Among all sarcoidosis patients, the group of patients with cardiac sarcoidosis and no treatment had the best mean value of the covered distance. At the same time, however, their mean age was lower by 6 years than the age of the remaining sarcoidosis patients. The 6MWT distance was closely related to speed of walking. The younger patients with cardiac sarcoidosis who received no treatment walked faster than older patients from the group with treated cardiac sarcoidosis, and from the group without cardiac involvement.

There was no difference in distance between men and women in the group of patients with cardiac sarcoidosis and GC treatment, and in the group without cardiac involvement.

Patients with cardiac sarcoidosis and coexisting diabetes mellitus (n = 3) covered shorter distances than patients with cardiac sarcoidosis and no disturbances of carbohydrate metabolism (393 ± 43 vs. 564 ± 94 m; p = 0.01), but they also had significantly higher BMI (32.4 ± 4.9 vs. 26.1 ± 3.6; p = 0.03). None of the remaining comorbidities had a significant influence on 6MWT distance.

Heart rate and oxygen saturation

There was a significantly smaller increase in heart rate in the first minute (ΔHR1) of the baseline test in the group of patients with cardiac sarcoidosis who were qualified for treatment, in comparison to patients without cardiac involvement and healthy volunteers (p = 0.01 and p = 0.0001, respectively) (Table 1, Figure 2). These patients had not been exercising on a regular basis, they did not have an increased ejection fraction of the heart, and
they were not on any beta-blockers or other antiarhythmic medications.

There was an interesting phenomenon observed in the group of patients qualified for treatment of cardiac sarcoidosis: the simultaneous decrease in heart rate and in oxygen saturation (at the same minute of walking drop of oxygen saturation, e.g. from 96 to 89%, and drop of heart rate, e.g. from 125 to 100 bpm).

In patients qualified for treatment due to cardiac sarcoidosis, deeper desaturation and shorter distance were noted than in the remaining groups (Table 1, Figure 3).

Dyspnoea

The Borg scale was used to assess the degree of dyspnoea during 6MWT. The majority of patients (n = 35) did not have any sensation of dyspnoea directly before or after the test – Borg scale scores were 0. Only single patients reported dyspnoea. None of the healthy volunteers reported shortness of breath either before or after the test (Borg score 0).

Impact of treatment with glucocorticosteroids

There was an improvement or complete remission of cardiac changes in all patients with cardiac sarcoidosis treated with GC, seen on MRI after 12 months. In follow-up 6MWT, as compared with baseline test, significant acceleration of heart rate in the first minute was noted (p = 0.02). It could be clearly seen even after 1 month of the therapy. Figure 4 depicts those changes, and figure 5 shows the mean values and standard deviation of heart rate in the first minute of the tests performed during the treatment.

The treatment also resulted in a decrease of the desaturation degree, especially during the first

Figure 2. Heart rate during six-minute walk test in all groups; s — cardiac sarcoidosis, with treatment; nl — cardiac sarcoidosis, with no treatment; b — pulmonary sarcoidosis with no cardiac involvement; z — control group

Figure 3. Saturation during six-minute walk test in all groups; s — cardiac sarcoidosis, with treatment; nl — cardiac sarcoidosis, with no treatment; b — pulmonary sarcoidosis with no cardiac involvement; z — control group

Figure 4. Heart rate during six-minute walk test in patients with cardiac sarcoidosis (n = 11) before (m0), after 1 month treatment (m1), after 6 months’ treatment (m6) and after 12 months’ treatment (m12)

Figure 5. Heart rate in the first minute six-minute walk test during treatment in patients with cardiac sarcoidosis (ANOVA Friedman), p = 0.02; hr1 — heart rate in the first minute before treatment; 2hr1 — after 1 month treatment; 3hr1 — after 6 months’ treatment; 4hr1 — after 12 months’ treatment
minute of the test (Figure 6), and in significant improvement of the distance \((p = 0.05)\) (Figure 7).

**Discussion**

6MWT has been used for the assessment of exercise capacity, monitoring of treatment, and rehabilitation outcomes in many cardio-pulmonary conditions for many years. Its usefulness in determining functional status, prognosis, and effectiveness of treatment and rehabilitation has been reported for example in chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and pulmonary hypertension. It is helpful in patient evaluation before lung transplantation, after pacemaker implantation, or before surgical treatment of intermittent claudication [14–17].

Only a few publications have been dedicated to the usefulness of 6MWT in sarcoidosis [18–20]. There is no data on 6MWT, a simple, reproducible, inexpensive test which is easy for patients to perform, in cardiac sarcoidosis. As we showed in our study, 6MWT is a valuable test not only in the clinical assessment or treatment monitoring in patients with pulmonary sarcoidosis, but also in recognition and treatment monitoring in sarcoidosis of the heart.

Slower acceleration of heart rate in the first minute of the test in patients with cardiac sarcoidosis compared to the remaining participants in our study may indicate cardiac involvement in the course of sarcoidosis and the need for further investigations.

An additional benefit of applying 6MWT in cardiac sarcoidosis is the possibility of using it as a tool for monitoring the effectiveness of treatment. The use of MRI is limited due to its cost. Easier and less expensive tests like echo study or 6MWT are good alternatives.

The echo study has the advantage that it may be used in baseline evaluation and then for follow-up. 6MWT can give additional information about circulatory system performance during physical effort in cardiac sarcoidosis, especially when stress-echo cannot be performed.

The lack of echocardiographic features of heart sarcoidosis does not exclude cardiac involvement in the course of the disease. Our own experience, as well as that of other authors [21], shows that even in patients with very discreet or no heart pathology in echo study, features of the cardiac involvement may still be found on MRI.
The normal 6MWT distance for adults is 400–700 m. Many factors may cause its shortening: old age, female sex, obesity, short stature, respiratory tract diseases, cardiovascular diseases, musculoskeletal disorders, anaemia, or neurological conditions [13]. In patients with sarcoidosis the limitation in exercise capacity and exertional dyspnoea may be caused by interstitial fibrosis, obstruction, air-trapping, pulmonary hypertension, cardiac involvement (cardiomyopathy, heart failure, arrhythmias, and heart blocks), anaemia, involvement of the musculoskeletal system (myopathies, pains, arthritis, erythema nodosum), and neurological and psychiatric disorders (depression, fatigue) [18, 19].

Our results are in agreement with earlier studies [19], which reported a relationship between the age and length of 6MWT distance in healthy people, as well as in sarcoidosis patients. Factors that had an influence on the 6MWT result in our patients were: sex, age, BMI, and cardiac involvement. Among our patients, those with untreated cardiac sarcoidosis had the longest 6MWT distance, but on the other hand they were also younger - by six years on average – than the remaining patients. At the same time, patients with cardiac sarcoidosis had the most prominent exertional desaturation in comparison with other groups, which reflected more advanced pulmonary changes.

Comorbidities did not have any significant influence on 6MWT distance in our group. None of our patients suffered from ischaemic heart disease or heart failure.

The heart rate should accelerate during the exercise test. A lack of appropriate acceleration or deceleration of HR is a pathological symptom reflecting chronotropic insufficiency, and may indicate heart injury [22]. We excluded physical training, increased cardiac ejection fraction, medications (i.e. beta-blockers), or other cardiac conditions as reasons for poor HR acceleration seen during 6MWT in patients with cardiac sarcoidosis. Inadequate HR acceleration and HR deceleration during exercise in those patients may reflect disturbances related directly to heart sarcoidosis. An additional argument supporting this thesis is an improvement during GC therapy. According to Fletcher et al. [22], chronotropic insufficiency of the heart is associated with higher risk of death in patients with cardiovascular diseases; hence, obtaining an improvement in exercise capacity and appropriate HR with the GCs therapy in cardiac sarcoidosis seems to be very important.

In the group of patients with heart sarcoidosis treated with GCs, reduction or complete remission of changes in follow-up cardiac MRI was seen after 12 months of treatment. An improvement in HR acceleration in the first minute of exercise and an improvement in exertional desaturation were also noticed.

Interestingly, an improvement in oxygen saturation in patients treated with GCs for cardiac involvement was observed after the first month of therapy (further treatment had no significant influence on it); while the maximum effect of GCs on HR was seen after 6–12 months of treatment (Figures 4, 6). This observation, as well as the findings on MRI, indicate the need for continuation of GCs treatment in cardiac sarcoidosis for at least one year.

The drop in oxygen saturation, also seen in the first minute of 6MWT, is most likely related to the lack of adequate HR acceleration. It probably mirrors the inhibition of ‘expected’ increase of cardiac output. It is difficult to explain this phenomenon. It probably involves serious disturbances of the function of the sinus node and autonomic nervous system. The subsidence of this phenomenon on GCs treatment may be used as an important indicator of the treatment efficacy.

We consider the discovery of smaller increase in HR in the first minute of 6MWT, a phenomenon of a ‘reverse adaptation’ of the circulatory system to physical effort in patients with cardiac sarcoidosis, to be the most important finding of our study.

**Conclusions**

1. 6MWT is useful in both preliminary and follow-up assessments of patients with cardiac sarcoidosis.
2. In the first minute of 6MWT the acceleration of HR was significantly smaller and oxygen saturation drop was greater in patients with heart involvement in the course of sarcoidosis, in comparison to patients with sarcoidosis limited to the lungs, and to healthy volunteers.
3. In the course of GCs treatment for cardiac sarcoidosis significant regression of cardiac involvement on MRI was coupled with greater HR acceleration and smaller oxygen desaturation in the first minute of 6MWT.

**Conflict of interest**

The authors declare no conflict of interest.

**Piśmiennictwo**