

Cardiac sarcoidosis: worse pulmonary function due to left ventricular ejection fraction?

A case-control study

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Abstract

Dyspnea and exercise intolerance are usually attributed to pulmonary disease in sarcoidosis patients. However, cardiac involvement may also be responsible for these symptoms. Data regarding the impact of heart involvement on lung function in cardiac sarcoidosis (CS) is limited.

The aim of study was to compare the results of pulmonary function tests (PFTs) in patients with and without heart involvement. We performed a retrospective analysis of PFTs in a group of sarcoidosis patients both with and without heart involvement evaluated by cardiovascular magnetic resonance (CMR) study. The study was performed in the period between May 2008 and April 2016.

We included data of sarcoidosis patients who underwent testing for possible CS (including CMR study) at a national tertiary referral center for patients with interstitial lung diseases. All patients had histopathologically confirmed sarcoidosis and underwent standard evaluation with PFTs measurements including spirometry, plethysmography, lung transfer factor ($T_{L,CO}$), and 6-minute walking test (6MWT) assessed using the most recent predicted values.

We identified 255 sarcoidosis patients (93 women, age 42 ± 10.7 y): 103 with CS and 152 without CS (controls). CS patients had significantly lower left ventricular ejection fraction (LVEF; 56.9 ± 7.0 vs 60.4 ± 5.4 , $P < .001$). Any type of lung dysfunction was seen in 63% of CS patients compared with 31% in the controls ($P = .005$). Ventilatory disturbances (obstructive or restrictive pattern) and low $T_{L,CO}$ were more frequent in CS group (52% vs 23%, $P < .001$ and 38% vs 18% $P < .01$ respectively). CS (OR = 2.13, 95% CI: 1.11–4.07, $P = .02$), stage of the disease (OR = 3.13, 95% CI: 1.4–7.0, $P = .006$) and LVEF (coefficient = -0.068 ± 0.027 , $P = .011$) were independent factors associated with low FEV₁ but not low $T_{L,CO}$. There was a significant correlation between LVEF and FEV₁ in CS group ($r = 0.31$, $n = 89$, $P = .003$). No significant difference in 6MWT between CS patients and controls was observed.

Lung function impairment was more frequent in CS. Lower LVEF was associated with decreased values of FEV₁. Relatively poor lung function may be an indication of cardiac sarcoidosis.

Abbreviations: 6MWT/D = 6-minute walking test/distance, CI = confidence interval, CMR = cardiac magnetic resonance, CS = cardiac sarcoidosis, ECG = electrocardiography, ECHO = echocardiography, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, GLI = global lung initiative, LLN = lower limit of normal, LVEF = left ventricular ejection fraction, $T_{L,CO}$ = transfer factor for carbon monoxide, TLC = total lung capacity.

Keywords: 6-minute walk test, cardiac sarcoidosis, obstruction, pulmonary function tests, restriction, sarcoidosis

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1. Introduction

Sarcoidosis is an idiopathic systemic disease characterized by the presence of non-caseating granulomas in the involved organs (usually respiratory system with or without intrathoracic lymph nodes).^[1] Pulmonary involvement may be present in various manifestation ranging from sporadic disseminated granulomas to more extensive consolidations, and in some cases fibrosis. Pulmonary function tests (PFTs) results may be impaired in sarcoidosis patients, however the ventilatory disturbances of either airway obstruction or restriction are less frequent than parenchymal related diffusion and lung compliance abnormalities.^[2] For many years, the clinical significance of mild to moderate changes in PFTs was perceived as ambiguous.^[3] Despite the potentially reversible nature of sarcoidosis (with possible spontaneous regression in the lung) progressive pulmonary sarcoidosis is one of the main causes of poor prognosis, including death, in the course of the disease.^[4,5]

The second most common cause of death (first in Japanese sarcoidosis patients population) is heart involvement.^[6] The prognosis of cardiac sarcoidosis (CS) is related to extent and site of involvement in the heart, however sudden cardiac death, due to

malignant ventricular tachyarrhythmias, or advanced heart block can occur even in previously asymptomatic patients.^[7]

CS may lead to heart failure and reduced left ventricular ejection fraction (LVEF) and may be also a reason for lung function impairment.^[8]

The heart and lung involvement are the most significant contributors to fatal outcome due to sarcoidosis.^[9] In previous studies the relationship between pulmonary status and CS have not been well defined. We are aware of only one study where impaired PFTs and/or progression of radiological chest imaging was mentioned.^[10]

The health care system in Poland has established that almost all patients with suspected interstitial lung diseases (ILDs), including sarcoidosis, are referred for diagnostic procedures to hospitals. The National TB & Lung Diseases Research Institute in Warsaw, Poland serves as the regional referral center for patients with sarcoidosis and other ILDs. Due to a research project of active looking for patients with heart involvement (screening using CMR study) performed in our institution for 3 years and our previously gathered (and published) data, we have collected data from a large number of CS patients as well as a large number of patients in whom CMR study was negative.^[11,12] This gave us an opportunity to compare 2 well defined, large groups of sarcoidosis patients with reference to lung function and 6-minute walking test (6MWT).

The main purpose of the study was to assess and compare results of PFTs in patients with and without heart involvement using the most recently obtained spirometry and 6MWT results. We hypothesized, that due to cardiac involvement, CS patients may have lower lung function and exercise capacity (expressed in 6MWT).

2. Material and methods

2.1. Patients

We performed a retrospective analysis of PFTs and 6MWT in the group of biopsy-proven sarcoidosis patients with and without heart involvement confirmed in the cardiovascular magnetic resonance (CMR) study.

The study covered period from May 2008 to April 2016 and was performed in 2 departments in our hospital. Analysis gathered data of 1615 sarcoidosis patients (see the flowchart in Fig. 1). During this period, we identified 103 patients with CS confirmed by CMR. As a control group, we used data of 152 sarcoidosis patients with negative CMR study results collected in screening study for CS performed from October 2012 to September 2015. The indication for CMR investigation was screening in prospective group which we reported in 2016^[11] and clinical suspicion of CS in patients taken from retrospective large cohort data.^[12]

All patients diagnosed or followed due to sarcoidosis underwent standard evaluation containing: clinical assessment, laboratory tests, radiological chest examination, standard 12-lead electrocardiography (ECG), abdominal ultrasonography, ophthalmology assessment (or other consultation of specialist or additional tests, if needed), and PFTs with 6MWT (in patients without contraindications). Chest x-ray was scored using Scadding stage. Echocardiography (ECHO), 24h-Holter monitoring were also collected. We collected demographic information, medical history, including comorbidities and medical treatment. Patients with recognized other cardiac diseases,

particularly coronary artery disease, which could influence the CMR imaging and making it non-conclusive, were not included in the final study. None of patients included in the analysis was treated due to sarcoidosis at the time of CMR and PFT investigations and for a year prior to the study.

2.2. Cardiac magnetic resonance imaging

All patients provided informed consent prior to CMR study. CMR studies were performed using 1.5T scanner (Siemens, Avanto SQ-engine T-class Tim [76 × 32]) with a dedicated 32-channel cardiac coil. Study protocol consisted of function, edema, and late gadolinium enhancement (LGE) imaging. LGE image were evaluated visually for enhancement regions. Presence as well as location of LGE were analyzed.

CMR findings were considered to be positive for active CS if both increased signal intensity on T2-weighted sequences (edema) and delayed contrast enhancement were present. The final diagnosis for active myocarditis due to CS disease was confirmed by positive CMR test without evidence of other reasons for such abnormalities.^[13] This is consistent with the current recommendations of the World Association of Sarcoidosis and other Granulomatous (WASOG) guidelines.^[14]

Left ventricular ejection fraction (LVEF) was assessed according to Society for Cardiovascular Magnetic Resonance (SCMR) 2008 and 2013^[15] recommendations on dedicated workstation with advanced cardiac package (Argus Cardiac Function, Siemens Inc., Erlangen, Germany).

2.3. Pulmonary function tests and 6-minute walking test

PFTs included spirometry, plethysmography, and T_{LCO} measurements using the single breath method. Tests were done using a MasterScreen system (software version 4.65; Jaeger, Würzburg, Germany). ATS/ERS 2005 guidelines were followed for all lung function measurements.^[16–18] We used reference values from GLI-2012^[19] for spirometry, from ECCS/ERS 1993^[20] for lung volumes, and from GLI-2017 for T_{LCO} ^[21], defining the lower limit of normal at the level of -1.645 SD, and grading the severity of ventilatory impairment and T_{LCO} reduction according to the ATS/ERS 2005 guidelines.^[22]

The 6MWT was conducted in accordance with ATS guidelines.^[23] All patients exhibited resting oxygen saturation $>90\%$ at the beginning of the walking test (none of them needed oxygen supplementation). Heart rate (HR), blood pressure, oxygen saturation, and Borg dyspnea index were recorded at the beginning and end of the 6 minute walk. The total distance walked (6-minute walk distance—6MWD, in meters) was documented at the end of the test and additionally heart rate and oxygen saturation were recorded at the end of every minute of the test.

We calculated distance-saturation product (DSP), which was defined by Lettieri et al^[24] as a result of the 6MWD multiplied by the lowest oxygen saturation.

2.4. Statistical analysis

Descriptive data was presented as mean \pm standard deviation. All comparisons and analyses of PFTs results were conducted with values normalized for age, size, and sex expressed as Z-score (difference from the predicted value divided by standard deviation in reference population). Group comparisons were

made using paired t tests for independent samples. The incidence ratios were presented as numbers of patients in groups and percentages. The Pearson Chi-squared test was used to check for differences in the prevalence of observations. A Pearson product-moment correlation coefficient was computed to assess the relationship between continuous variables. Logistic regression analysis was used to build the model of association between disease stage, smoking, disease duration, LVEF, and presence of cardiac involvement as predictors and the impaired lung function (low FEV₁ or low $T_{L,CO}$) as an outcome. The odds ratios with 95% confidence intervals and P -values were presented. To examine the associations of the lung function variables with the LVEF, multiple linear regression analyses were performed with smoking, cardiac involvement, and disease duration and stage as possible explanatory variables. The coefficient of determination (R^2), standardized effect sizes (β) for each lung function parameter with 95% confidence intervals and P -values were presented.

All statistical analyses were performed using STATISTICA (data analysis software system StatSoft, Inc. 2010), version 9.1 and MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 1993–2018).

2.5. Ethics approval and consent to participate

This study is a retrospective analysis of de-identified data. All procedures performed in study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Study was also approved by National TB & Lung Diseases Research Institute Ethic Committee (approval no. KB-108/2012).

3. Results

During the 7-year period, over 1600 sarcoidosis patients were examined in our hospital. Among them we have identified 265 sarcoidosis patients, all Caucasian, who underwent tests for the diagnosis of CS (including CMR study). Patients were assigned to 2 subgroups: 103 patients with diagnosis of CS (CMR positive) and 152 controls with sarcoidosis without cardiac involvement (CMR negative)—see the flowchart in Fig. 1 for details. All patients had histopathologically confirmed sarcoidosis. The careful review of clinical data revealed that only 2 patients in screening study^[11] and 10 patients from cohort study^[12] were treated in the past. In all cases the period of treatment was finished earlier than 12 months before CMR study. Patients' characteristic is given in Table 1.

Patients in the CS group had lower FEV₁, FVC, and FEV₁/FVC than controls (see Table 2). This was consistent with a combined obstructive and restrictive difference. There was also a greater transfer factor impairment for the CS group.

Almost two-thirds of CS patients (63%) had one or more lung function disturbance compared with one-third (31%) of the control group. Spirometry detectable ventilatory disturbances (obstruction or possible restrictive pattern) were twice as frequent in CS group (52% vs 23%, $P < .001$) with the dominant role of airway obstruction.

Low $T_{L,CO}$ results were observed significantly more frequently in CS patients than in controls (38% vs 18% $P < .01$). Prevalence of different types of lung function disturbances and overlapping of them in CS and control group are presented in Fig. 2.

In purpose of finding the association between disease stage, smoking status, disease duration, LVEF, and presence of cardiac involvement as predictors of impaired lung function (low FEV₁ or low $T_{L,CO}$) as an outcome, we have built the models using logistic regression analysis. It revealed that presence of CS (OR=2.13,

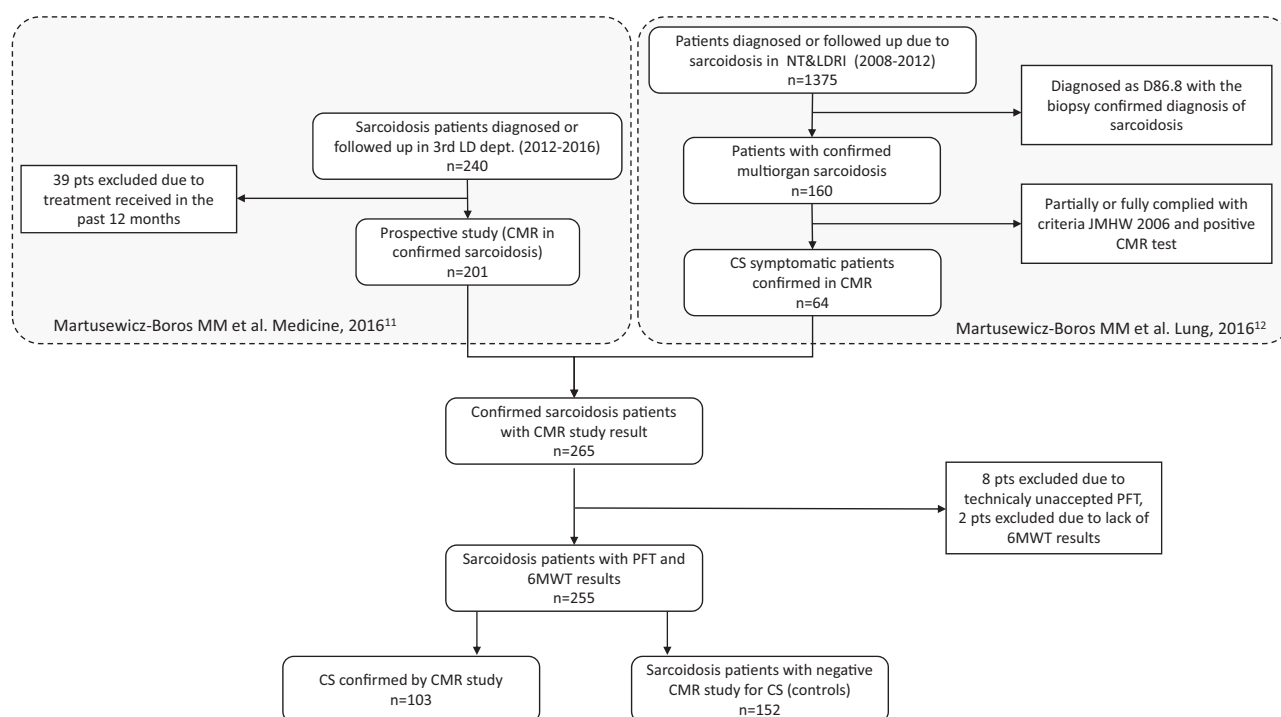


Figure 1. The flowchart of the study.

Table 1**Study group characteristics.**

	Cardiac sarcoidosis (n = 103)	Controls (n = 152)	P-value
Age	42.4 ± 11.3	41.7 ± 10.3	.3
Males/Females	73%/27%	57%/43%	.01
Patients in scadding stages 1/2/3 (%)	16/82/5 (15.5/79.6/4.9)	36/112/4 (23.7/73.7/2.6)	.2
Patients treated in the past*	7 (6.8%)	5 (3.3%)	.19
Time from the diagnosis to CMR investigation, mo	29.9 ± 42.1	18.0 ± 36.8	.018
% of ever-smokers and cigarette consumption (pack-years)	44.7%	37.5%	.25
	11.5 ± 9.7	9.5 ± 7.3	.24
Extrathoracic [†] sarcoidosis	52 (50.5%)	36 (23.7%)	.0001
LVEF in CMR study	56.9 ± 7.0 (n = 89)	60.4 ± 5.4	.00001

Cardiac sarcoidosis means positive in CMR study, controls—patients with sarcoidosis but without heart involvement in CMR study. CMR = cardiac magnetic resonance, LVEF = left ventricular ejection fraction.

* Treated due to pulmonary sarcoidosis and treatment finished >12 months before CMR (see explanation in text).

[†] Sarcoidosis in locations other than in chest (lung, intrathoracic lymph nodes, heart are excluded).

Bold values are statistically significant (<0.05).

95% CI: 1.11–4.07, $P=.02$), stage of the disease (OR=3.13, 95% CI: 1.4–7.0, $P=.006$) and LVEF (coefficient=−0.068 ± 0.027, $P=.011$) were independent factors associated with lung function disturbances expressed as low FEV₁. In respect to low T_{LCO} results, only more advanced stage of the disease (OR=2.66, 95% CI: 1.24–5.7, $P=.012$) and presence of cardiac involvement (OR=2.29, 95% CI: 1.21–4.36, $P=.011$) signifi-

Table 2**Lung function in cardiac sarcoidosis patients and controls (Z-scores, %pred, % of abnormal results, and % of cases in severity grades).**

	Cardiac sarcoidosis	Controls	P-value
FEV ₁	n = 103	n = 152	
(Z-score)	−1.28 ± 1.66	−0.66 ± 1.29	.001
(% pred)	82.8 ± 21.8	91.1 ± 16.8	.0007
% cases < LLN	39.8%	17.8%	.00009
FVC	n = 103	n = 152	
(Z-score)	−0.65 ± 1.51	−0.27 ± 1.09	.019
(% pred)	91.7 ± 18.9	96.6 ± 13.9	.019
% cases < LLN	26%	11%	.001
FEV ₁ /FVC	n = 103	n = 152	
(abs.)	0.72 ± 0.11	0.76 ± 0.08	.001
(Z-score)	−1.16 ± 1.36	−0.71 ± 1.1	.004
% of obstructives	37%	17%	.0004
Mild	27%	13%	
Moderate	7%	1%	
Moderately severe	3%	1%	
Severe		2%	
TLC	n = 101	n = 152	
(Z-score)	−0.17 ± 1.51	0.03 ± 1.15	.222
(%pred.)	98.4 ± 15.6	100.7 ± 12.7	.199
% of restrictives	18%	7%	.0097
T_{LCO}	n = 101	n = 151	
(Z-score)	−1.35 ± 1.73	−0.84 ± 1.38	.01
(%pred.)	83.4 ± 19.4	89.5 ± 18.4	.013
% of cases < LLN	38%	18%	.0041
Mild	33%	13%	
Moderate	5%	5%	
Severe	1%	1%	

abs. = absolute value; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LLN = lower limit of normal; TLC = total lung capacity; T_{LCO} = transfer factor for carbon monoxide; Z-score = result expressed as difference from mean divided by standard deviation value for reference population. Airway obstruction classified according to FEV₁: mild >70%pred., moderate 60–69%pred., moderately severe 50–59%pred., severe 35–49%pred. T_{LCO} classified: mild: 60%pred. and <LLN, moderate: 40–60%pred., severe <40%pred.

Bold values are statistically significant (<0.05).

cantly increased the chance for abnormal results. A multiple regression analysis (with FEV₁ and T_{LCO} expressed as Z-score) confirmed these findings. A significant regression equation was found ($F(6, 229) = 5.432$, $P < .0001$), with an R^2 of 0.125. Patients' FEV₁ (Z-score) was significantly associated only with stage of the disease ($\beta = -0.692 \pm 0.2$, $P = .001$) and LVEF ($\beta = 0.041 \pm 0.016$, $P = .01$). Presence of CS did not reach satisfactory significance level, but the trend was observed ($\beta = -0.361 \pm 0.201$, $P = .07$). Similar analysis referring to T_{LCO} revealed also significant regression equation ($F(6, 228) = 3.493$, $P = .003$), with an R^2 of 0.084. Patients' T_{LCO} (Z-score) was significantly associated with stage of the disease ($\beta = -0.72 \pm 0.216$, $P = .001$) and smoking ($\beta = -0.4 \pm 0.2$, $P = .05$) but not with LVEF. The presence of lung function disturbances, particularly airway obstruction was not associated with fact of cigarette smoking.

As the LVEF was significantly different in CS and controls we looked for associations between lung function and cardiac performance. We observed significant correlation between LVEF and FEV₁ in CS group ($r = 0.31$, $n = 89$, $P = .003$) while not in controls (Fig. 3).

We did not find significant differences in 6MWD expressed in absolute values as well as transformed to Z-score between CS patients and controls (in general and in various disease stages), although we observed greater decrease in oxygen saturation and slower heart rate in the sixth minute of test in the CS group (see Table 3).

A multiple linear regression was calculated looking for association between 6MWD, smoking, cardiac involvement, disease duration, stage, and LVEF. There were no significant relationships in build model ($F(5, 220) = 1.183$, $P = .32$), with an R^2 of 0.026.

4. Discussion

Sarcoidosis is a multi-organ disease but the most common manifestations are lung and surrounding lymph nodes abnormalities.^[1,25] Although isolated CS may occur,^[26] majority of CS patients has pulmonary disease. Because of increased awareness and improved diagnostic methods, a higher detection rate of CS has been observed.^[8]

Heart and lung involvement are the most significant contributors to mortality in sarcoidosis. To date, the relationship between cardiac and pulmonary disease has often been overlooked.^[5] Many studies of CS do not describe the PFTs and we are not aware of any previous study focused on pulmonary function comparing CS-positive versus CS-negative patients.

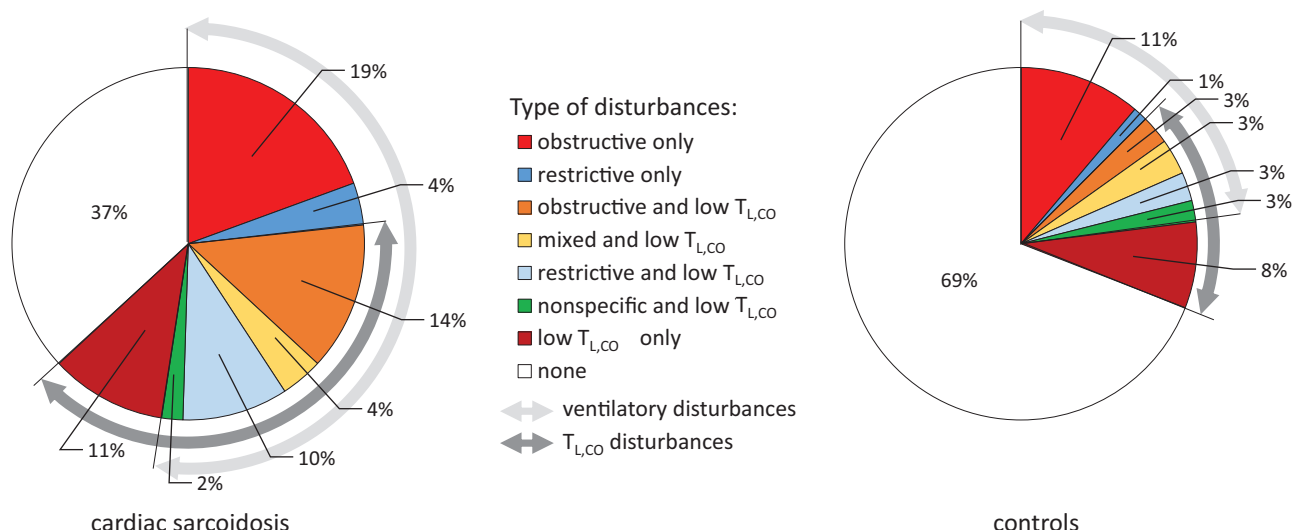


Figure 2. Prevalence of lung function disturbances in cardiac sarcoidosis and control patients (percentages). Obstructive: $FEV_1/FVC < LLN$, restrictive: $TLC < LLN$ and $FEV_1/FVC > LLN$, mixed: $TLC < LLN$ and $FEV_1/FVC < LLN$; nonspecific: $FEV_1 < LLN$, $FVC < LLN$, $FEV_1/FVC > LLN$ and $TLC > LLN$; low T_{LCO} means $< LLN$. FEV_1 =forced expiratory volume in 1 second, FVC =forced vital capacity, LLN =lower limit of normal, TLC =total lung capacity.

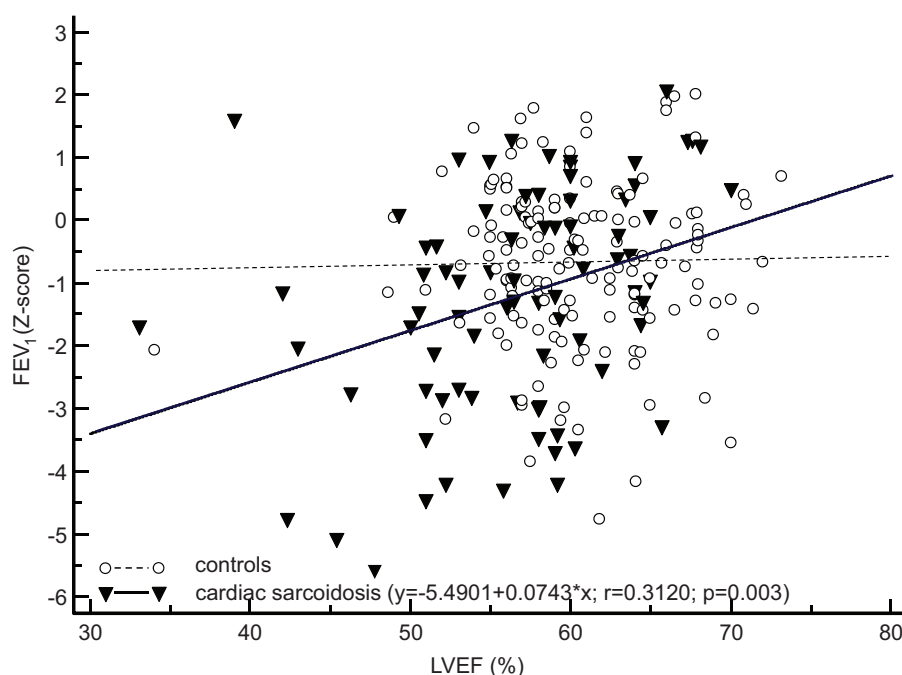


Figure 3. FEV_1 (Z-score) in relation to left ventricular ejection fraction (LVEF) in cardiac sarcoidosis and controls patients. FEV_1 =forced expiratory volume in 1 second.

While analyzing the role of ECG in predicting CS, Darlington et al.^[27] found correlation between presence of parenchymal lung infiltrates and abnormal ECG, however they did not show results of PFTs in the studied cohort. Chapelon et al.^[28] in a retrospective study, described abnormal PFTs in 13 from 39 (33%) patients with CS (without comparison to control group), 2 with obstructive, and 11 with restrictive patterns. Decreased T_{LCO} was noted in 46% of cases. Mehta et al.^[10] in univariate analysis, found a higher FVC but not FEV_1 (expressed as %predicted) to be a predictor of CS, however multivariate analysis did not

confirm this finding. Nagai et al.^[29] found no significant difference in VC% predicted between LGE positive and negative group. In the study of Handa et al.^[30] patients with CS diagnosed according to Japanese guidelines, had T_{LCO} %predicted significantly lower than controls.

Our groups were different, since CS patients were more likely to be male. This is in consistency with our previous observations.^[11,12] CS patients had lower LVEF which is to be expected as this form of the disease may lead to heart failure, but only in 3 of our patients observed LVEF values were below 40%.^[8]

Table 3**Six-minute walking test (6-MWT) results in cardiac sarcoidosis and control group.**

	Cardiac sarcoidosis (n = 103)	Controls (n = 152)	P-value
6MWD (m)	591.5 ± 113.1	584.4 ± 82.3	.57
6MWD (z-score)	-0.27 ± 0.36	-0.25 ± 0.26	.54
Number (%) of 6MWD < LLN	8 (7.8%)	9 (5.9%)	.55
Initial HR (b/min)	80.8 ± 15	79.6 ± 12.7	.49
Final HR (b/min)	128.3 ± 17.7	133.3 ± 13.4	.014
Initial Sat O ₂ (%)	96.8 ± 1.1	97 ± 1.1	.24
Lowest Sat O ₂ (%)	93.8 ± 4.1	94.9 ± 2	.011
Number of patients with Sat O ₂ min < 92% during exercise	13 (13.3%)	8 (5.7%)	.042
Number of patients with Sat O ₂ min < 90% During exercise	10 (10.2%)	3 (2.1%)	.0065
Drop of Sat O ₂	2.96 ± 3.71	2.09 ± 1.71	.016
% cases with drop of SatO ₂ > 4 mmHg	24.5%	12.8%	.02
Initial Borg score	0.04 ± 0.31	0.01 ± 0.17	.49
Final Borg score	0.35 ± 1	0.14 ± 0.77	.07
DSP (m%)	556.8 ± 114.6	554.9 ± 80.7	.88

6MWT = 6-minute walk test; 6MWD = 6-minute walk distance; CS(+) = patients with diagnosis of cardiac sarcoidosis; DSP = distance-saturation product (results of the 6MWD multiplied by the lowest oxygen saturation); HR = heart ratio; Sat. = saturation.

Bold values are statistically significant (<0.05).

Two-thirds of our CS patients had impaired lung function compared with half of the control group. Ventilatory disturbances were twice more frequent in CS group and airway obstruction was usually responsible for this. Significant differences were observed in stage 2 disease, which made up 3 quarters of our investigated group. Results from stage 3 sarcoidosis patients are of limited value due to small number of cases (only 9 in both subgroups). The prevalence of reduced FEV₁/FVC below LLN (37%) in CS patients is much higher than in controls (17.1%), but also as compared with general population of patients with sarcoidosis (11.7% in general and 13% in stage 2).^[12] In our study, airway obstruction was not associated with smoking, age, and sex. In a previous report, smoking, age, and sex were important predictors for airway obstruction for African Americans, but not Caucasians.^[31] One of possible explanations for the association between CS and airway obstruction may be bronchial hyperreactivity often observed in sarcoidosis patients,^[32] which could have been augmented due to lower LVEF.^[33]

Airway obstruction frequently detected in CS patients is regarded as one of the poor prognostic factors in the course of the disease.^[4] We can only speculate that airway obstruction is partially associated with cardiac involvement and poorer LVEF. It may factor into increased risk of bad outcome of the disease.

Restrictive pattern (TLC below LLN) was also found more than twice as often in CS than in our controls (17.4% vs 7%) and general sarcoidosis population (7% in previously published data).^[12] However, differences in Z-scores for TLC were not significant between analyzed groups. Reduction in FEV₁ correlated with lower values of LVEF in CS patients, which can be a partial explanation of observed phenomenon. Data published by Andrea et al^[34] and Baum et al^[35] showed, that even patients with well preserved LVEF may have impaired lung function.

Reduction in FEV₁ can be seen in obstructive and restrictive lung diseases, and it is therefore considered as a universal ventilatory disturbance index. We performed multiregression analysis of the FEV₁ and other factors. Cardiac sarcoidosis was an independent predictor of reduced FEV₁. Moreover, there was also a correlation with lower values of LVEF and FEV₁ in CS patients.

A low T_{LCO} was also more frequent than in our controls (38% vs 18%) and in the general sarcoidosis population.^[12]

Current analysis revealed significantly worse results of PFTs in CS patients. In contrast, the differences in 6MWT results were small and their clinical value in predicting CS is limited. The most significant contrast was seen in desaturation below 90% (10% in CS patients vs 2% in controls), but due to study design lack of desaturation cannot be regarded as negative predictor of CS. Moreover, the presence of abnormalities in 6MWT may have many causes depending on different factors such as lung function, general cardiac status, and respiratory and skeletal muscle strength.^[36,37] Mean values of DSP in our sarcoidosis cohort was rather high, compared with other studies, which suggests a good general functional status.^[37,38] However, we did not find differences in DSP between CS-positive and -negative group.

4.1. Strengths and limitations of the study

Our analysis was performed in 2 large, well defined groups of CS-positive and CS-negative Caucasian sarcoidosis patients. The diagnosis or exclusion of cardiac involvement was based on CMR imaging, one of the best methods for detecting cardiac involvement in sarcoidosis.^[39,40] Moreover, this method allows one to reliably measure the left ventricular ejection fraction. For assessing PFTs, we wanted to avoid well known biases and misclassifications, so we used transformation to Z-scores and the latest reference values for spirometry and T_{LCO}.^[19,21,22]

This was a retrospective analysis, thus a prospective study would be useful to confirm and generalize our observations. We realize that the collected cohort of patients was partially preselected. We chose patients who met the criteria established for this study research, specifically excluding those who did not have PFTs or had undergone CMR.

Taking into account the results of our analysis, we concluded that obstructive and restrictive patterns as well as T_{LCO} impairment were more frequent in CS vs. patients without cardiac involvement. Ventilatory lung function impairment expressed as low FEV₁ was associated with more advanced stage of the disease and lower values of LVEF. T_{LCO} impairment was associated with advanced stage and smoking rather than

cardiac performance. 6MWD was not significantly affected in sarcoidosis patients irrespective of cardiac involvement.

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