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Evaluation of findings in non-invasive cardiac diagnostics with imaging and functional tests of the lungs in sarcoidosis

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ABSTRACT

Introduction: Sarcoidosis is a systemic inflammatory granulomatous disease most commonly found in the lungs, and less frequently in other organs such as the lymph nodes or the heart.

Materials and methods: In this observational study, 62 adult patients with pulmonary sarcoidosis were enrolled. Their preexisting pulmonary diagnostics, including imaging and functional tests, were analyzed. Additionally, non-invasive cardiological diagnostics: electrocardiography (ECG), Holter electrocardiography (Holter ECG), transthoracic echocardiography (TTE) and laboratory tests were performed.

Results: The most common findings were numerous ventricular arrhythmias (20.34%), pericardial effusion (40.32%), and left ventricular relaxation disorders (29.03%). A positive correlation was found between the duration of sarcoidosis and wall motion score index (WMSI; p = 0.026), as well as between the stage of sarcoidosis in chest X-ray/computed tomography (CXR/CT) and tricuspid regurgitation peak gradient – TRPG (p = 0.001). An inverse correlation was found between diffusion lung capacity for carbon monoxide (DLCO) and the stage of sarcoidosis (p = 0.037), forced vital capacity (FVC) and ventricular systolic asynchrony (p = 0.044), both forced expiratory volume in 1 s (FEV1) and FVC, and the width of the pulmonary trunk (p = 0.046 and p = 0.045), both FEV1 and FVC, and the width of the right ventricle (p = 0.036 and p = 0.04), and total lung capacity (TLC) and the width of the left atrium (p = 0.007).

Conclusions: A longer duration of the disease was associated with more advanced heart involvement. Higher stages of sarcoidosis were associated with more frequent cardiac changes.

Keywords: sarcoidosis; cardiac sarcoidosis; pulmonary function tests; echocardiography; ECG; Holter ECG monitor.

INTRODUCTION

Sarcoidosis is a systemic inflammatory granulomatous disease characterized by the accumulation of CD4+ lymphocytes in various tissues, most commonly in the lungs [1]. The etiology remains ambiguous, involving multiple hypotheses concerning both the genetic basis of the disease and the influence of environmental factors [2]. It primarily affects young individuals, mainly before the age of 50. Approximately 70% of cases occur between the ages of 25–40, with another peak after the age of 50, predominantly among women. While it can occur worldwide, it is more prevalent among Swedes, Danes, and African Americans [2, 3]. Women account for 45–60% of sarcoidosis cases [4, 5].

The acute onset of sarcoidosis, known as Löfgren's syndrome, was described by Swedish physician Sven Löfgren. It presents with fever, arthritis (mainly in the ankles), erythema nodosum, and bilateral enlargement of the pulmonary cavities due to lymphadenopathy, visible in chest X-ray (CXR) [1, 6]. Initially, the disease can often be asymptomatic or present with mild symptoms such as: dyspnea, fatigue, cough, anorexia, muscle fatigue, and exercise limitation. Besides the lungs, sarcoidosis can affect the spleen, liver, muscles, bones, kidneys, central nervous system (CNS), and heart [2, 3]. Heart and CNS involvement, which may be the first manifestations, affect up to 10% of patients [2]. In Western countries, the most common cause of death is progressive pulmonary fibrosis, leading to respiratory failure or pulmonary hypertension. In Japan, cardiac sarcoidosis (CS) is the leading cause of death, accounting for nearly 77% of cases [2, 7]. Pulmonary symptoms such as: cough, shortness of breath, and chest pain affect 30–53% of patients [7, 8, 9].

Only 5% of patients with CS present with site-specific symptoms. Granulomas are most often located in the left ventricle walls, especially around the basilar part of the interventricular septum, leading to atrioventricular (26–68%) and intraventricular (12–61%) blocks. Additionally, CS is associated with pericarditis, sick sinus syndrome, supraventricular (0–15%) and ventricular (2–42%) tachyarrhythmias, heart failure (10–30%), and sudden cardiac death (12–45%) [10]. Features of pulmonary hypertension are present in 5–15% of patients with sarcoidosis [11], with causes that may include pulmonary arterial

granulomas or pulmonary fibrosis [12]. Cardiac sarcoidosis is the leading cause of death in sarcoidosis overall, responsible for 13–25% of deaths in the USA and up to 85% in Japan [13, 14]. This is likely because clinical symptoms are present in only 5% of patients, and the disease can be diagnosed in only about 29% of living patients [15].

Echocardiographic changes may occur in up to 60% of patients with CS. Granulomas can be located in all layers of the cardiac muscle, most commonly in the walls of the left ventricle, where they may cause aneurysms, thinning and/or thickening of the heart walls, sometimes with hyperechoic foci forming a typical "pearl string" pattern [16]. Cardiac fibrosis leads to segmental contractility disorders and deterioration of left ventricular systolic function, which may result in dilated cardiomyopathy. Sarcoidosis is also associated with pericardial effusion (usually moderate) and valvular defects [10, 17]. The significant echocardiographic changes seen in sarcoidosis make echocardiography a crucial test in diagnosing CS.

Moreover, increased serum cardiac markers such as high-sensitive troponin T (TnT-hs) and natriuretic peptide-proB type (NT-proBNP) are observed in CS [18, 19, 20, 21]. These markers may reflect myocardial involvement and/or the development of heart failure.

Advanced diagnostic tests are also used to diagnose CS, including endomyocardial biopsy, technetium or gallium scintigraphy of cardiac perfusion, positron emission computed tomography, and cardiac magnetic resonance (CMR), which is considered the diagnostic standard in Europe [18]. Cardiac magnetic resonance is particularly useful because it can reveal numerous pathologies associated with the disease, such as: pericardial effusion, reduced ejection fraction, valvular disease, heart wall abnormalities, and late gadolinium enhancement.

Currently, it is recommended that every patient diagnosed with sarcoidosis undergo basic cardiological diagnostics, including 12-lead electrocardiography (ECG), Holter electrocardiography (Holter ECG) monitoring, and transthoracic echocardiography (TTE) [22, 23]. This study focused on non-invasive cardiological diagnostics of patients with sarcoidosis to demonstrate the relationship between cardiological and pulmonary imaging and functional tests.

MATERIALS AND METHODS

The authors conducted an observational study analyzing pre-existing medical data and performing non-invasive cardiological diagnostics (ECG, Holter ECG monitoring, TTE) along with laboratory tests: creatine kinase-MB (CKMB), TnT-hs and NT-proBNP. Patients diagnosed with pulmonary sarcoidosis through histopathological evaluation were enrolled in the study. The available previous medical history regarding pulmonary diagnostics was reviewed. Imaging tests included CXR and CT. Functional tests, such as spirometry and body plethysmography, were also utilized for the analysis. The final database comprised 30 body plethysmographies, 41 spirometries, and 55 CXRs and/or CTs. All the aforementioned diagnostics were performed over a 2-year period (Fig. 1).

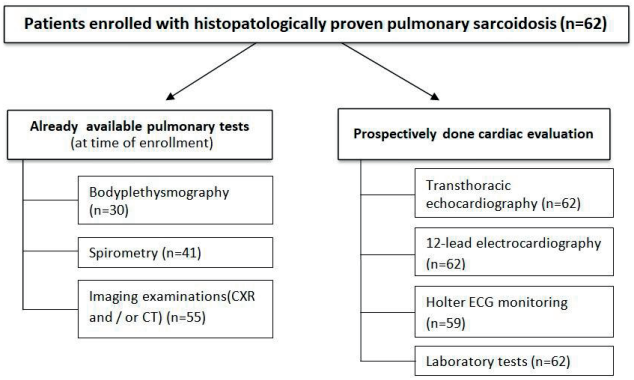

FIGURE 1. Flowchart of the research

Based on the available documentation and radiological findings, the staging of pulmonary sarcoidosis (I–IV) was determined according to the Siltzbach classification [24]. For this study, the spirometry parameters analyzed were forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC), expressed as a percentage of the norm. The FEV1/FVC ratio was also calculated, with a value of <0.7 indicating bronchial obstruction. Based on these parameters, the results were classified as normal, obstruction, or suspected restriction. It was also verified whether the response to the bronchodilator test was performed during the examination and its result (positive or negative) [25, 26].

In the body plethysmography study, the parameters considered were total lung capacity (TLC) and diffusion lung capacity for carbon monoxide (DLCO). Both parameters were analyzed quantitatively (expressed as a percentage of the predicted value) and qualitatively (normal/below normal). According to current recommendations, values above 80% of the predicted value for DLCO and above the fifth percentile of the predicted value for TLC were adopted as the norm [16, 25, 26].

Patients were also subjected to ECG, Holter ECG monitoring, and TTE. A total of 62 12-lead ECGs and 62 TTEs were performed. However, due to the resignation of 3 patients, Holter ECG monitoring was conducted in only 59 patients.

While interpreting both resting electrocardiographic records and Holter examinations, emphasis was placed on analyzing the heart axis, leading rhythm, atrioventricular and intraventricular conduction disorders (including Q wave), features of atrial and ventricular hypertrophy, changes in the ST-T segment and arrhythmias.

In TTE, parameters were recorded according to the current recommendations of the Polish/European Society of Cardiology (PCS/ESC), with particular emphasis on findings most frequently occurring in sarcoidosis with cardiac involvement [27, 28]. The echocardiographic parameters assessed included left atrial volume index (LAVI), left ventricular mass index (LVMI), and relative wall thickness (RWT). Using these parameters,

left ventricular geometry was assessed with the following possible results:

- normal geometry (LVMI and RWT in norm),
- concentric remodeling (LVMI in norm, RWT over norm),
- concentric hypertrophy (LVMI and RWT over norm),
- eccentric hypertrophy (LVMI over norm, RWT in norm).

Left ventricular ejection fraction was assessed using both the Simpson method and 3-dimensional (3D) echocardiography. Additionally, the wall motion score index (WMSI) was calculated based on the segment contractility. The left ventricle was divided into 17 segments, with each segment assigned a score as follows:

- normokinesis – 1 point,
- hypokinesis – 2 points,
- akinesis – 3 points,
- dyskinesia – 4 points.

The number of points was summed and divided by the number of assessed segments to calculate the WMSI. Diastolic function was assessed according to the guidelines [27, 28] in the following categories:

- without diastolic dysfunction: early filling velocity mitral inflow (E)/ atrial filling velocity (A) >1, deceleration time (DecT) <220 ms,
- impaired relaxation pattern: E/A <1, DecT >220 ms, early diastolic mitral annulus velocity (e') septal <8 cm/s, lateral <10 cm/s,
- pseudonormalization of mitral inflow pattern: E/A >1, DecT 140–220 ms, e' septal <8 cm/s, e' lateral <10 cm/s, E/e' >13,
- restrictive mitral inflow pattern: E/A >2, DecT <140 ms, e' septal <8 cm/s, e' lateral <10 cm/s, E/e' >13.

Intraventricular systolic asynchrony was assessed according to the guidelines of PCS/ESC [28], using complementary methods:

- qualitative echocardiographic parameters used to assess intraventricular systolic asynchrony:
  - the presence of short-term movement of the interventricular septum towards left ventricular lumen (septal flash),
  - characteristic apical rocking,
- quantitative parameter assessed by echocardiography:
  - the delay time of the posterior wall relative to the ventricular septum assessed along the long axis in parasternal projection in M-Mode. A time greater than 130 ms indicates intraventricular contraction asynchrony.

The presence and amount of pericardial effusion were assessed according to current guidelines for the diagnosis and treatment of pericardial diseases [17]:

- lack of fluid in the pericardial sac,
- a small amount of fluid (up to 1 cm),
- a moderate amount of fluid (1–2 cm),
- a large amount of fluid (>2 cm).

The probability of pulmonary hypertension was assessed as low, moderate, or high according to current guidelines [29].

Ethical considerations

The study received permission from the Bioethics Committee of the District Medical Chamber in Szczecin on March 30, 2017 (decision No. 04/KB/VI/2017).

Data collection and study populations

Patients were selected randomly based on their availability during telephone recruitment. Sixty-two patients were enrolled in the study. All of them had histopathologically proven pulmonary sarcoidosis, had given their informed consent for participation, and were over 18 years old. The exclusion criteria were: probable lack of cooperation from patients, concomitant heart disease (e.g., congenital/acquired heart diseases, ischemic and non-ischemic cardiomyopathy), active infections (e.g., infective endocarditis, pneumonia), acute diseases (e.g., acute heart failure, acute coronary syndrome), and active neoplastic disease.

The study group consisted of 21 women and 41 men diagnosed with sarcoidosis between 2003–2019 in the Department of Pulmonology and the Department of Thoracic Surgery and Transplantation of the Pomeranian Medical University in Szczecin (PMU). Patients were recruited, and cardiological tests were performed between 2017–2020 at the Department of Cardiology of the PMU.

Statistical analysis

All analyses were performed using licensed software Statistica 13 (StatSoft, Inc., Tulsa, OK, USA). Continuous variables are presented as mean, standard deviation, median, counts, and percentage. The normality of the distribution of the examined variables was assessed using the Shapiro–Wilk test. Levene's test was used to assess the homogeneity of variance. The correlation coefficient was assessed using Spearman's rank test. A p-value of ≤0.05 was considered significant.

RESULTS

Sixty-two patients diagnosed with sarcoidosis were enrolled in the study. Demographic data, comorbidities, family history, medications taken, and symptoms are presented in Tables 1, 2, 3, respectively.

TABLE 1. Demographic data, comorbidities and family history of patients

Demographic data		
Sex – n (%)	women	21 (33.9%)
	men	41 (66.1%)
Age – years (Me; Q1–Q3)		43.0; 38.0–51.0
Weight – kg (Me; Q1–Q3)		85.0; 76.0–98.0
Height – cm (Me; Q1–Q3)		177.0; 168.0–172.0
BMI (Me; Q1–Q3)		27.1; 24.6–30.7

TABLE 1. Demographic data, comorbidities and family history of patients

Demographic data		
AB0 – n (%)	0	17 (33.3%)
	A	20 (39.2%)
	AB	6 (11.8%)
	B	8 (15.7%)
Rh – n (%)	Rh–	11 (21.6%)
	Rh+	40 (78.4%)
Smoking history – n (%)		34 (54.8%)
Present smoking – years (Me; Q1–Q3)		9.0; 2.5–10.0
Drug use history – n (%)		11 (17.7%)
Age at diagnosis of sarcoidosis – years (Me; Q1–Q3)		40.0; 34.0–48.0
Duration of sarcoidosis – months (Me; Q1–Q3)		21.5; 10.0–41.0
Sarcoidosis locations diagnosed before enrollment		
Pulmonary sarcoidosis – n (%)		62 (100.0%)
Cardiac sarcoidosis – n (%)		5 (8.1%)
Splenic sarcoidosis – n (%)		4 (6.5%)
Neurosarcoidosis – n (%)		1 (1.6%)
Hepatic sarcoidosis – n (%)		1 (1.6%)
Skin sarcoidosis – n (%)		1 (1.6%)
Comorbidities		
COPD – n (%)		2 (3.2%)
Asthma – n (%)		4 (6.5%)
Stroke – n (%)		1 (1.6%)
Prediabetes – n (%)		5 (8.1%)
Diabetes melitus I – n (%)		1 (1.6%)
Diabetes melitus II – n (%)		7 (11.3%)
Dyslipidemia – n (%)		20 (32.3%)
Arterial hypertension – n (%)		20 (32.3%)
Heart failure – n (%)		3 (4.8%)
Arrhythmias – n (%)		6 (9.7%)
Chronic kidney diseases – n (%)		2 (3.2%)
Thyroid diseases – n (%)	all	11 (17.7%)
	hypothyroidism	8 (72.7%)
	hyperthyroidism	2 (18.2%)
	euthyroid	1 (9.1%)
Family history		
Cancer – n (%)	all	32 (51.6%)
	lung cancer	8 (12.9%)
	breast cancer	7 (11.5%)
Sarcoidosis – n (%)		5 (8.1%)

ABO – blood group; BMI – body mass index; COPD – chronic obstructive pulmonary disease; Me – median; n – number of patients; Rh – rhesus blood factor

TABLE 2. Pharmacological treatment among patients at the time of enrollment

Drugs	
Beta-blockers – n (%)	16 (25.8%)
ACE–I – n (%)	8 (12.9%)
Sartans – n (%)	4 (6.5%)
Diuretics – n (%)	5 (8.1%)
CCBs – n (%)	8 (12.9%)
Aldosterone rec. antagonists – n (%)	2 (3.2%)
Statins/fibrates – n (%)	5 (8.1%)
Oral antidiabetic drugs/insulin – n (%)	8 (12.9%)
Antiplatelet agents – n (%)	3 (4.8%)
Inhalation drugs – n (%)	8 (12.9%)
Oral glucocorticosteroids – n (%)	7 (11.3%)

ACE-I – angiotensin-converting enzyme inhibitor; CCBs – calcium channel blockers; n – number of patients

TABLE 3. Symptoms/ailments at the time of enrollment

Symptoms throughout the disease	
Joint pain/swelling – n (%)	35 (56.5%)
Cough – n (%)	33 (53.2%)
Dyspnoea – n (%)	33 (53.2%)
Sweating – n (%)	21 (33.9%)
Low-grade fever/ fever – n (%)	19 (30.7%)
Weakness – n (%)	18 (29.0%)
Erythema nodosum – n (%)	17 (27.4%)
Löfgren's syndrome – n (%)	16 (25.8%)
Chest pain – n (%)	14 (22.6%)
Palpitations – n (%)	11 (17.7%)
Skin pain/oedema – n (%)	5 (8.1%)
Somnolence – n (%)	4 (6.5%)

n – number of patients

Selected results of the pulmonary function tests and imaging are presented in the table below (Tab. 4).

Results of cardiological examinations and laboratory tests are presented in Tables 5 and 6.

TABLE 4. Selected results of pulmonary studies in patients with sarcoidosis

Pulmonary function tests and lung imaging	
DLCO – % (Me; Q1–Q3)	83.1; 73.0–99.8
Norm DLCO >80% of its value – n (%)	18 (58.1%)
TLC – % (Me; Q1–Q3)	90.0; 82.0–95.0
Norm TLC >5 percentile of predicted value – n (%)	24 (80.0%)
FEV1%norm (Me; Q1–Q3)	92.0; 82.1–98.0
FVC%norm (Me; Q1–Q3)	94.8; 85.0–102.0
FEV1/FVC (Me; Q1–Q3)	0.8; 0.78–0.85

TABLE 4. Selected results of pulmonary studies in patients with sarcoidosis

Pulmonary function tests and lung imaging		
Reversibility test positive – n (%)		1 (8.3%)
Interpretation	norm – n (%)	36 (87.8%)
	obturation – n (%)	3 (7.3%)
	suspicion of restrictions – n (%)	2 (4.9%)
Staging (CXR/CT)	Me; Q1–Q3	2.0; 1.0–2.0
	1 – n (%)	19 (34.6%)
	2 – n (%)	32 (58.2%)
	3 – n (%)	3 (5.5%)
	4 – n (%)	1 (1.8%)

CT – computed tomography; CXR – chest X-ray; DLCO – diffusion lung capacity for carbon monoxide; FEV1 – forced expiratory volume in 1 s; FVC – forced vital capacity; Me – median; n – number of patients; TLC – total lung capacity

TABLE 5. Selected parameters from the electrocardiography and Holter electrocardiography studies in patients with sarcoidosis

ECG		
Axis – n (%)	normal	56 (90.3%)
	left deviation	3 (4.8%)
	right deviation	3 (4.8%)
Abnormal Q wave – n (%)		1 (1.6%)
Atrioventricular block I° – n (%)		4 (6.5%)
Bundle branch block – n (%)	RBBB	1 (1.6%)
	LBBB	2 (3.2%)
Left atrial enlargement – n (%)		3 (4.8%)
Right atrial enlargement – n (%)		1 (1.6%)
Right ventricular hypertrophy – n (%)		1 (1.6%)
Extrasystole – n (%)	supraventricular	2 (3.2%)
	ventricular	2 (3.2%)
Holter monitor ECG		
Pause ≥2 s – n (%)		1 (1.7%)
Supraventricular arrhythmias – n (%)	SVE	50 (84.8%)
	nsSVT	11 (18.6%)
Ventricular arrhythmias – n (%)	VE	40 (67.8%)
	VE ≥100	12 (20.3%)
	VE ≥1000	3 (5.1%)
	VE number (Me; Q1-Q3)	9.0; 3.0–164.0
	multifocal ventricular extrasystoles (≥2 morphologies)	8 (13.6%)
	ventricular bigeminy + trigeminy	7 (11.9%)
	ventricular pairs	4 (6.8%)
	nsVT	4 (6.8%)
	complex ventricular arrhythmias (pairs + nsVT)	7 (11.9%)

ECG – electrocardiography; Holter ECG monitor – 24-hour registration electrocardiography; LBBB – left bundle branch block; Me – median; n – number of patients; nsSVT – nonsustained supraventricular tachycardia; nsVT – nonsustained ventricular tachycardia; RBBB – right bundle branch block; SVE – supraventricular extrasystole; VE – ventricular extrasystole

TABLE 6. Selected echocardiography parameters and laboratory findings in patients

TTE results		
Aorta – mm (Me; Q1–Q3)		35.0; 32.0–37.0
Left atrium	PLAX diameter – mm (Me; Q1–Q3)	37.0; 34.0–40.0
	LAV – mL (Me; Q1–Q3)	47.0; 40.0–56.0
	LAVI – mL/m² (Me; Q1–Q3)	23.9; 19.5–30.9
Right atrium	area – cm² (Me; Q1–Q3)	13.9; 11.9–14.9
	volume – mL (Me; Q1–Q3)	34.0; 27.0–35.0
IVSd – mm (Me; Q1–Q3)		10.0; 9.0–11.0
LVPWd – mm (Me; Q1–Q3)		9.0; 8.0–9.0
LVIDd – mm (Me; Q1–Q3)		48.0; 45.0–52.0
RWT (Me; Q1–Q3)		0.36; 0.33–0.40
LVMI – g/m² (Me; Q1–Q3)		74.7; 61.5–88.7
Left ventricular geometry – n (%)	normal geometry	51 (82.3%)
	concentric hypertrophy	1 (1.6%)
	concentric remodelling	7 (11.3%)
	eccentric hypertrophy	3 (4.8%)
Right ventricular end-diastolic diameter (basal measurement in 4-chamber view) – mm (Me; Q1–Q3)		33.0; 29.0–36.0
Pulmonary trunk diameter – mm (Me; Q1–Q3)		21.0; 19.0–21.0
Anterior wall of right ventricle – mm (Me; Q1–Q3)		4.0; 4.0–4.0
Pulmonary acceleration time ≤105 ms – n (%)		5 (9.1%)
TRPG – mmHg (Me; Q1–Q3)		17.0; 17.0–20.3
Probability of pulmonary hypertension – n (%)	low	60 (96.8%)
	intermediate	2 (3.2%)
	high	0 (0.00%)
WMSI (Me; Q1–Q3)		1.0; 1.0–1.0
EF (%)	Simson (Me; Q1–Q3)	65.0; 60.0–70.5
	3D (Me; Q1–Q3)	60.0; 57.0–62.0
Ventricular systolic asynchrony – n%		5 (8.1%)
S' (m/s)	septum (Me; Q1–Q3)	0.08; 0.07–0.08
	lateral (Me; Q1–Q3)	0.08; 0.07–0.10
Diastolic dysfunction – n (%)	normal diastolic function	44 (71.0%)
	relaxation dysfunction	18 (29.0%)
	pseudonormal mitral inflow pattern	0 (0.0%)
	restrictive mitral inflow pattern	0 (0.0%)
Pericardial effusion – n (%)	without	37 (59.7%)
	<1 cm	25 (40.3%)
	>1.0	0 (0.0%)
HFpEF – n (%)		5 (8.1%)

TABLE 6. Selected echocardiography parameters and laboratory findings in patients

Laboratory tests	
CKMB – U/L, n < 25 (Me; Q1–Q3)	15.5; 13.0–19.0
Upper limit of CKMB norm – n (%)	6 (9.7 %)
TnT-hs – ug/L, n < 0.014 (Me; Q1–Q3)	0.003; 0.001–0.005
Upper limit of TnT norm – n (%)	3 (4.8 %)
NT-proBNP – pg/mL, n < 125 (Me; Q1–Q3)	45.2; 20.5–75.3
Upper limit of NT-proBNP norm – n (%)	7 (11.3 %)

CKMB – creatine kinase isoenzyme MB; TTE – transthoracic echocardiography; EF – ejection fraction; HFpEF – heart failure with preserved ejection fraction; IVSd – interventricular septum thickness in diastole; LAV – left atrium volume; LAVI – left atrial volume index; LVIDd – left ventricular internal end-diastolic diameter; LVMI – left ventricular mass index; LVPWd – left ventricular posterior wall thickness in diastole; Me – median; n – number of patients; NT-proBNP – natriuretic peptide-proB-type; PLAX – parasternal long axis; RWT – relative wall thickness; S' – peak systolic annular velocity; TnT-hs – troponin t-high sensitive; TRPG – tricuspid regurgitation peak gradient; WMSI — wall motion score index

Due to the multitude of parameters obtained, Table 7 shows the correlations of selected pulmonary and cardiological parameters that showed statistical significance ($p \leq 0.05$). A positive correlation was found between the duration of sarcoidosis and the WMSI index ($R = 0.283$, $p = 0.026$), as well as between the stage of sarcoidosis in CXR/CT and tricuspid regurgitation peak gradient – TRPG ($R = 0.656$, $p = 0.001$).

An inverse correlation was found between DLCO and the stage of sarcoidosis in CXR/CT ($R = -0.383$, $p = 0.037$), between the value of FVC and ventricular systolic asynchrony ($R = -0.317$, $p = 0.44$), between FEV1 and the width of the pulmonary trunk ($R = -0.325$, $p = 0.046$), between FVC and the width of the pulmonary trunk ($R = -0.327$, $p = 0.045$), between FEV1 and the width of the right ventricle ($R = -0.333$, $p = 0.036$), between FVC and the width of the right ventricle ($R = -0.447$, $p = 0.04$), and between TLC and the width of the left atrium ($R = -0.494$, $p = 0.007$).

The study did not show a statistically significant correlation between age and the size of the left atrium.

TABLE 7. Statistically significant (p < 0.05) correlations of pulmonary and cardiac results in patients with sarcoidosis (Spearman's rank test)

A pair of correlations	R	p
FVC (%) & intraventricular systolic asynchrony	–0.317	0.044
FEV1 (%) & pulmonary trunk diameter (mm)	–0.325	0.046
FVC (%) & pulmonary trunk diameter (mm)	–0.327	0.045
FEV1 (%) & right ventricular end-diastolic diameter (basal measurement in 4-chamber view) – mm	–0.333	0.036
DLCO (%) & CXR/CT (stage)	–0.383	0.037
FVC (%) & right ventricular end–diastolic diameter (basal measurement in 4-chamber view) – mm	–0.447	0.004
TLC (%) & left atrium PLAX diameter (mm)	–0.494	0.007
Duration of sarcoidosis (months) & WMSI	0.283	0.026
FVC (%) & S' septum (m/s)	0.365	0.031
CXR/CT (stage) & TRPG (mmHg)	0.656	0.001

CT – computed tomography; CXR – chest X-ray; DLCO – diffusion lung capacity for carbon monoxide; FEV1 – forced expiratory volume in 1 s; FVC – forced vital capacity; p – statistical significant; PLAX – parasternal long axis; R – correlation coefficient; TLC – total lung capacity; TRPG – tricuspid regurgitation peak gradient; WMSI – wall motion score index

DISCUSSION

Heart involvement in sarcoidosis has long been considered rare. However, recent studies, including autopsy reports, indicate it occurs more frequently (20–58%) [23, 30]. Simultaneous involvement of the heart and lungs is a significant factor for increased mortality [14]. Therefore, it is recommended that every patient diagnosed with sarcoidosis undergo basic cardiological diagnostics [23, 31].

In the study group, an intermediate heart axis was most commonly found in ECG (90.3%). Additionally, 3 patients had bundle branch block, and all of them exhibited intraventricular asynchrony on ECG. The Holter ECG monitor study frequently diagnosed numerous ventricular arrhythmias (20.3%) and multifocal ventricular extrasystoles (12.9%).

Echocardiographic examinations often showed enlargement of the left atrium (24.2%) and diastolic dysfunction (29.0%) – Figure 2, while the majority of patients (82.3%) had a normal left ventricular structure. A high-resistance pulmonary flow profile was found in 5 patients, and pulmonary trunk dilatation was observed in 3 patients. Intraventricular systolic asynchrony was found in 5 patients, mild diastolic dysfunction in 18 patients, and a small amount of fluid (<1 cm) in the pericardial sac in 25 patients (40.3%). The frequent presence of pericardial effusion and a small amount of fluid are consistent with current reports [10, 18].

Based on available laboratory tests and echocardiographic findings, 5 patients were diagnosed with heart failure with preserved ejection fraction (HFpEF) according to current guidelines [32]. The results obtained in this group are consistent with previous reports [10, 11, 17, 18, 31].

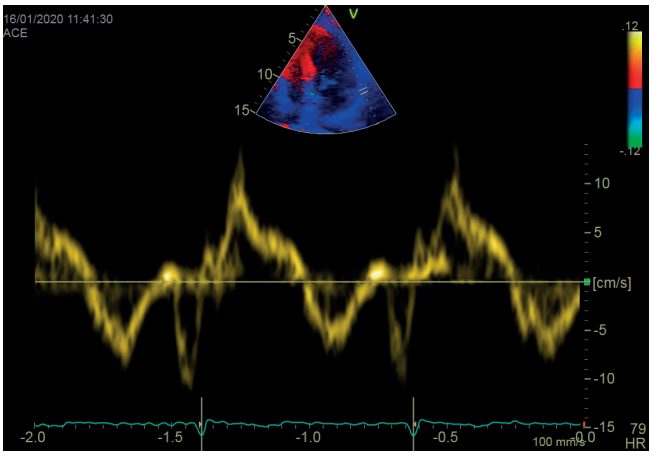

FIGURE 2. Tissue Doppler echocardiography showing reduced early diastolic velocity of the lateral mitral annulus (8 cm/s), indicating diastolic dysfunction

So far, little research has compared the results of cardiac and pulmonary examinations among patients with sarcoidosis. In this study, a significant negative correlation was found between FEV1, FVC, and the width of the pulmonary trunk and the right ventricle ($R = -0.325$, $p = 0.046$; $R = -0.327$, $p = 0.045$; $R = -0.333$, $p = 0.036$; and $R = -0.447$, $p = 0.04$, respectively). Both greater width of the pulmonary trunk and right ventricle are indicators

of pulmonary hypertension. Sarcoidosis, like all obstructive disorders, predisposes patients to the development of pulmonary hypertension, which confirms the obtained results [29].

Additionally, an inverse correlation was found between the FVC value and intraventricular systolic asynchrony (R = –0.317, p = 0.44) and a positive correlation between FVC and septal s' (R = 0.365, p = 0.031). Similar relationships among patients with sarcoidosis could not be found in the currently available literature. However, in the general population, researchers indicate that lung dysfunction (determined by FEV1, FVC, and FEV1/FVC) is associated with deterioration of systolic and diastolic heart function [33, 34]. Additionally, abnormal pulmonary parameters were more frequently observed in patients with cardiac involvement compared to those with pulmonary sarcoidosis alone [35].

This study found that with a longer duration of sarcoidosis, more advanced contractility disorders appear, as expressed by the WMSI (R = 0.283, p = 0.026; there were 9 patients with WMSI >1). This is consistent with previous literature, suggesting that the duration of sarcoidosis is an independent risk factor for disease progression [36] and heart involvement [37].

The study also found a negative correlation between TLC and the width of the left atrium (R = –0.494, p = 0.007). Although current literature has not found conclusive data comparing these parameters, studies among the general population have indicated worse results in cardiological tests and a predisposition to heart failure, including HFpEF, in patients with lung dysfunction [33]. Left atrial volume is one of the criteria for the diagnosis of HFpEF, which may partially explain the observed dependencies [18]. Moreover, according to the work of Kasapkara et al., left atrial volume parameters are early markers of heart involvement in sarcoidosis [38], and the FEV1/FVC index itself is highlighted by other researchers as a risk factor for CS [39] and a poor prognostic factor [40].

It is also worth noting that this study did not show a statistically significant correlation between age and the size of the left atrium, probably due to the relatively young study group (Me age: 43 years).

Another finding in our study was that a higher sarcoidosis stage was associated with lower DLCO levels (R = –0.383, p = 0.037). Similar relationships, indicating worse results in functional tests, including DLCO, in patients with a higher stage of the disease, have been reported in the general population of patients with sarcoidosis [41]. A positive correlation was also found between the stage of sarcoidosis and the TRPG level (R = 0.656, p = 0.001). Sarcoidosis can lead to pulmonary hypertension, and an increased gradient across the tricuspid valve is one of its indicators [31]. Worse cardiological examination results may occur at higher stages of lung sarcoidosis, which confirms the obtained results [33, 34]. Diaz-Guzman et al. demonstrated a more frequent occurrence of pulmonary hypertension among patients with a higher stage of sarcoidosis [42]. Additionally, higher right systolic ventricular pressure (RVSP) was found in patients with CS compared to healthy individuals [43].

Limitations

We recognize several limitations in this study. First, the pulmonary records were analyzed retrospectively, so not all patients had both spirometry and body plethysmography performed. Additionally, some pulmonary tests were considered outdated, having been conducted more than 2 years before the cardiological diagnosis. Another limitation was the relatively low number of patients, which precluded more advanced statistical analyses (e.g., multifactorial analyses). Furthermore, the research spanned 2016–2021, during which period the ESC guidelines changed, causing some difficulties in implementing the study protocol. Finally, 3 patients withdrew from the Holter-ECG examination for personal reasons.

CONCLUSIONS

Among patients with sarcoidosis, the most common findings were multiple ventricular arrhythmias, pericardial effusion, and left ventricular relaxation disorders. Longer duration of sarcoidosis was associated with more advanced heart involvement, as assessed by morphological and functional markers in echocardiography. Additionally, higher stages of the disease, as defined by pulmonary functional and radiological tests, were associated with morphological and functional changes observed in non-invasive heart diagnostics.

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