

## THE EFFECT OF GLOBAL LONGITUDINAL STRAIN ON IMPAIRED SIX-MINUTE WALK TEST PERFORMANCE IN PATIENTS WITH SARCOIDOSIS

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**ABSTRACT.** *Background:* Sarcoidosis is a multisystem and granulomatous disease associated with impaired functional capacity as a result of pulmonary and cardiac involvement. Factors adversely effecting functional capacity in patients with sarcoidosis have not been systematically assessed including myocardial strain imaging on echocardiography which enable to diagnose subclinical cardiac dysfunction. We aimed to evaluate the effect of left and right ventricular global longitudinal strain (GLS) on submaximal exercise capacity in patients with sarcoidosis who do not have clinically manifest cardiac involvement. *Methods:* Extracardiac biopsy proven 56 patients with sarcoidosis and 26 controls were included consecutively. Submaximal exercise capacity of the subjects was assessed with six-minute walk test (6 MWT). Pulmonary function tests and standard transthoracic and two-dimensional speckle tracking echocardiography were performed to the all subjects. Linear regression analysis was performed to find independent predictors of 6 MWT. *Results:* Fifty-six patients (18% male) with a mean age of  $52.5 \pm 10.7$  years were included. Patients with sarcoidosis had low 6 MWT performance and higher New York Heart Association classes and NT-proBNP levels. There were no significant differences between controls and patients with sarcoidosis in parameters of pulmonary function test. Biventricular GLS levels and biatrial reservoir and conduit function values were lower and systolic pulmonary artery pressure (SPAP) was significantly higher in patients with sarcoidosis as compared with controls. Older age and higher SPAP were found as independent predictors of poor 6 MWT performance. *Conclusion:* Although biventricular GLS levels were lower in the patients with sarcoidosis, only age and SPAP elevations were independent predictors of the submaximal exercise capacity. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (1): 63-73)

**KEY WORDS:** global longitudinal strain, sarcoidosis, six-minute walk test, two-dimensional speckle tracking echocardiography, pulmonary hypertension

### INTRODUCTION

Sarcoidosis is a multisystem and granulomatous disease primarily effecting the lungs and lymph

nodes. Despite the unknown etiology, sarcoidosis stems from interaction of genetic and environmental factors (1-3). Although sarcoidosis often has good prognosis, coexistence of pulmonary and cardiac involvement and pulmonary hypertension (PHT) can deteriorate the clinical course. Cardiac manifestations of sarcoidosis are silent disease, heart block, ventricular tachycardia and dilated or hypertrophic cardiomyopathy. Clinically overt cardiac involvement occurs in 5% of patients in sarcoidosis. In addition, 25-30% of patients with sarcoidosis have asympto-

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matic cardiac involvement shown in autopsy series and newer imaging studies (4, 5). Several studies have used the myocardial strain imaging to detect asymptomatic cardiac involvement earlier (6-10). However, their prognostic roles need to be further clarified.

The six-minute walk test (6 MWT) is a simple, inexpensive and reproducible test to quantify the submaximal exercise capacity (11-14). Recent studies have shown that several factors are associated with poor 6 MWT performance including gender, forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV1) and systolic pulmonary artery pressure (SPAP) (15-18). However, no previous study has examined the relationship between subclinical cardiac dysfunction determined by two-dimensional (2D) speckle tracking echocardiography (STE) and 6 MWT performance in patients with sarcoidosis.

The aim of this study is to evaluate whether biventricular functions determined by 2D STE contribute to impaired submaximal exercise capacity quantified by six-minute walk distance (6 MWD) in patients with sarcoidosis.

## MATERIALS AND METHODS

### *Study population*

60 patients with biopsy proven extracardiac sarcoidosis were enrolled into the study. A comprehensive transthoracic echocardiography was performed to all study patients for evaluation cardiac functions. Patients who have impaired left ventricular (LV) function (ejection fraction < 50%), poor echogenicity, moderate to severe valvular pathology, history of coronary artery disease, diagnosis of malignancy, administration of chemotherapy, musculoskeletal disorders effecting 6 MWT performance were excluded from the study. One patient had impaired LV function, one patient had poor echogenicity, one patient had aortic valve prosthesis and one patient had history of coronary artery disease. Moreover, demographically similar 26 subjects were included as control group.

### *Measurements*

Clinical data including history of systemic hypertension or diabetes, organs involvement, duration of illness, steroid usage, New York Heart As-

sociation (NYHA) functional class, radiological stages (according to chest radiography) and results of pulmonary function testing, were recorded for all patients. Pulmonary function parameters were measured according to American Thoracic Society (ATS) and European Respiratory Society recommendations (19). The 6 MWT was conducted in accordance with ATS guidelines (20). Pulse oximetry saturations were recorded at the beginning and the end of the test. The total walking distances were recorded at the end of the test.

### *Standard and 2D Speckle Tracking Echocardiography*

A detailed transthoracic examination was performed using a commercially available system (Epiq 7, Philips Healthcare, Andover, MA, USA) equipped with a 3.5 mHz (S5-1) transducer. Images which have three cardiac cycles were digitally stored for offline analysis (Xcelera, Philips). Conventional left and right ventricular echocardiographic parameters were measured according to the standard recommendations (21). LV ejection fraction (EF) was calculated using the modified Simpson's biplane method (21). The LV mass was calculated by the formula recommended by the guidelines (21). Tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) fractional area change (FAC) and the lateral side tricuspid annular peak systolic velocity (S') were measured. RV free wall thickness was also measured according to guideline recommendations (21). Systolic pulmonary artery pressure (SPAP) was calculated using tricuspid valve regurgitation jet and estimated right atrial pressure by inferior vena cava size and collapsibility (21). LV diastolic function was assessed by transmitral inflow pulse-wave Doppler velocities and the lateral side of the mitral annular tissue Doppler velocities (22).

Myocardial strain analysis was performed to the all subjects as described previously (23-24). Apical (four-chamber, three-chamber and two-chamber views) and parasternal short-axis (the level of the base, papillary muscles, and apex) views were used to measure LV longitudinal and circumferential strain. End-systole has been accepted as aortic valve closure. End-diastolic regions of interest were traced on the endocardial cavity and the software tracked the border automatically. RV-focused apical four-chamber view were used for RV strain analyses. Longitudi-

nal strain values of basal, mid, and apical segments of RV free wall were measured. The average of RV free wall longitudinal strain values was accepted as RV global longitudinal strain (RV GLS). For the left atrial (LA) and right atrial (RA) strain analyses, apical four-chamber view were used. The value of peak early and late diastolic longitudinal strain was determined as LA and RA reservoir and conduit function. For interobserver and intraobserver variability, 10 patients were selected at random, measurements were reanalyzed by the same and another operator. The interobserver and intraobserver variabilities were 5.4 and 5.8 %, respectively in our study.

### Statistical Analysis

Data were analyzed using SPSS for Windows (Version 16.0; SPSS, Chicago, IL). One-sample Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Normal distributed data were presented as mean  $\pm$  SD, whereas variables not displaying normal distribution were presented as median with interquartile range. Categorical variables were summarized as percentages. For continuous variables, normal distributed parameters were compared by T-test, otherwise comparison was done by Mann-Whitney U-test. Categorical variables were compared by  $\chi^2$  test. Linear regression analyses were then performed to assess the independent correlates 6 MWD in the patient population. To estimate the significant correlated parameters Pearson correlation test were used. Then LV GLS, RV GLS, body mass index (BMI), E/e' ratio, age, SPAP, FVC and TAPSE were added into the multivariate analysis. P values < 0.05 were accepted significant.

## RESULTS

Data from 56 patients with sarcoidosis and 26 demographically similar controls were used in the analysis. Radiological stage, organ involvement, NYHA class of the patients with sarcoidosis were shown in Table 1. The median duration of the illness of patients with sarcoidosis was 4.0 (4.75) years and 22 (39.3%) of all patients were receiving steroid therapy. There were no differences between patients and controls regarding the prevalence of major comorbidities including diabetes, hypertension and smok-

**Table 1.** Baseline characteristics of the patients with sarcoidosis\*

Radiological stage	n (%)
0	2 (3.5%)
1	19 (33.9%)
2	24 (42.9%)
3	6 (10.7%)
4	3 (5.4%)
<b>Organ involvement</b>	
Pulmonary	54 (96.4%)
Skin	10 (17.8%)
Eye	5 (8.9%)
Neurologic	1 (1.8%)
<b>NYHA functional class</b>	
1	38 (67.8%)
2	10 (17.8%)
3	5 (8.9%)
4	3 (5.3%)

*NYHA: New York Heart Association Functional Classification*

\* Numerical variables are displayed as mean  $\pm$  standard deviation and categorical variables are displayed as percentages

ing (Table 2). There were also no differences between patients and controls in terms of pulmonary function test parameters (Table 2). The submaximal exercise capacity quantified by 6 MWD was significantly lower in patients with sarcoidosis. Although before and after test oxygen saturation levels were lower in patients, there were no significant differences for oxygen demand between patients and controls (Table 2). Patients with sarcoidosis had high NT-proBNP and uric acid levels (Table 2).

Between patients with sarcoidosis and controls, there were no differences regarding LV systolic functions (Table 3). However, LV diastolic function parameters such as mitral E/A ratio and transmitral E-wave DT were impaired in patients with sarcoidosis (Table 3). As shown, patients with sarcoidosis had significantly higher SPAP values, RV free wall thicknesses and lower TAPSE and RV FAC values (Table 3).

Table 4 shows the comparison of speckle tracking parameters between the two groups. Biventricular strain values were significantly lower in patients with sarcoidosis than in controls. LA and RA both reservoir and conduit functions were also significantly lower in sarcoidosis patients than controls.

**Table 2.** Demographic characteristics, cardiovascular risk factors and laboratory findings of the patients with sarcoidosis and controls\*

	Patients with sarcoidosis n = 56	Controls n = 26	P value
Age (years)	52.5 ± 10.7	48.8 ± 7.1	0.114
Gender male (n) (%)	10 (17.9)	6 (23.1)	0.565
BMI (kg/m <sup>2</sup> )	30.2 ± 5.2	28.2 ± 4.4	0.095
Hypertension (n) (%)	11 (19.6)	2 (7.7)	0.209
Diabetes (n) (%)	12 (19.6)	2 (7.7)	0.206
Smokers (n) (%)	6 (10.7)	7 (26.9)	0.101
NT-proBNP (pg/ml)	80.1 (223)	27.3 (49.8)	< <b>0.001</b>
Uric acid (mg/dl)	5.3 ± 1.6	4.2 ± 1.2	<b>0.003</b>
Creatinine (mg/dl)	0.75 ± 0.3	0.7 ± 0.1	0.317
Hemoglobin (gr/dl)	13.2 ± 1.7	13.3 ± 1.2	0.681
6 MWD (m)	425 ± 88.6	501.9 ± 48.9	< <b>0.001</b>
Before test O <sup>2</sup> saturation (%)	96.8 ± 3.3	98.6 ± 0.6	<b>0.009</b>
After test O <sup>2</sup> saturation (%)	96.6 ± 4.5	98.8 ± 0.5	<b>0.018</b>
O <sup>2</sup> demand	3 (5.4)	-	0.548
FEV 1 (%)	91.1 ± 20.2	98.3 ± 8.9	0.08
FVC (%)	94.1 ± 21.1	98.9 ± 11.7	0.28
FEV1/FVC ratio	0.97 ± 0.1	1.0 ± 0.1	0.157

**6 MWD:** six-minute walk distance; **BMI:** Body mass index; **FEV 1:** Forced expiratory volume in 1 second; **FVC:** Forced vital capacity; **NT-proBNP:** N terminal probrain natriuretic peptide; **O<sup>2</sup>:** Oxygen.

\* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

Independent predictors of 6 MWD were evaluated using linear regression analyses. Regression model included age, BMI, FVC, LV GLS, RV GLS, E/e' ratio, SPAP and TAPSE. Older age (beta coefficient -0.20, %95 CI for B -3.5 – 0.079, p = 0.04) and higher SPAP (beta coefficient -0.28, %95 CI for B -4.7 – 0.45, p = 0.018) were found to be independent predictors of low 6 MWD (Table 5).

## DISCUSSION

In this study, we demonstrated that the sub-maximal exercise capacity as assessed by 6 MWT was significantly reduced in patients with sarcoidosis compared with control population. Even in the absence of clinically overt cardiac dysfunction, biventricular and atrial functions as assessed by STE were significantly impaired in patients with sarcoidosis. Moreover, SPAP values were significantly increased

in patients with sarcoidosis despite the fact that there were no differences between patients with sarcoidosis and controls regarding pulmonary function tests. Finally, LV GLS and RV GLS were not independent predictors of 6 MWD in patients with sarcoidosis.

Recent studies have shown that several factors are associated with poor 6 MWT performance in patients with sarcoidosis (15-18). However, no previous study has examined the relationship between sub-clinical cardiac dysfunction using myocardial strain imaging and poor functional capacity. To the best of our knowledge this is the first study using STE to evaluate independent predictors of low 6 MWD in patients with sarcoidosis.

Previous studies have suggested that several parameters were associated independently with low 6 MWD. Almahad et al. demonstrated that FEV1 was an independent parameter of low 6 MWD (25). In same study, SPAP values measured by transthoracic echocardiography (TTE) were correlated with 6

**Table 3.** Conventional transthoracic echocardiographic findings of the patients with sarcoidosis and controls\*

	Patients with sarcoidosis n = 56	Controls n = 26	P value
LVEDD (mm)	45.0 ± 4.7	44.5 ± 3.9	0.59
LVESD (mm)	28.9 ± 5.8	27.6 ± 3.9	0.31
LV EF (%)	64.5 ± 8.8	66.5 ± 5.5	0.28
RV basal diameter (mm)	30.2 ± 3.7	29.3 ± 4.0	0.32
RV/LV ratio	0.72 ± 0.7	0.73 ± 0.7	0.66
LA diameter (mm)	33.7 ± 3.4	32.6 ± 3.4	0.16
LAA (cm <sup>2</sup> )	15.2 ± 3.5	14.6 ± 2.6	0.48
RAA (cm <sup>2</sup> )	12.9 ± 2.7	12.5 ± 2.4	0.48
Septum (mm)	10.0 ± 1.4	10.2 ± 1	0.54
PW (mm)	9.5 ± 1.1	9.7 ± 1.0	0.48
LV mass (gr)	149.4 ± 36.2	147.7 ± 28.9	0.83
RV wall thickness (mm)	4.9 ± 0.9	4.3 ± 0.4	<b>0.007</b>
Transmitral E velocity (cm/sec)	0.8 ± 0.2	0.8 ± 0.1	0.59
Transmitral A velocity (cm/sec)	0.8 ± 0.2	0.7 ± 0.1	0.18
Transmitral E-wave DT (msec)	199.3 ± 40.9	178.9 ± 24.9	<b>0.022</b>
Transmitral E/A ratio	1.0 ± 0.3	1.2 ± 0.3	<b>0.049</b>
Mitral lateral E' (cm/sec)	11.2 ± 3.7	13.0 ± 3.5	<b>0.03</b>
Mitral lateral A' (cm/sec)	10.8 ± 2.4	11.0 ± 3.0	0.747
Mitral lateral S' (cm/sec)	10.7 ± 2.9	10.6 ± 2.2	0.925
E/E' ratio (cm/sec)	7.5 ± 2.9	6.4 ± 1.6	0.079
Tricuspid lateral S' (cm/sec)	13.0 ± 2.4	13.9 ± 2.2	0.09
TAPSE (cm)	22.9 ± 4	25.5 ± 3.4	<b>0.005</b>
RV FAC (%)	45.4 ± 8.9	56.6 ± 7.9	<b>&lt; 0.001</b>
SPAP (mm Hg)	25.9 ± 9.5	18.8 ± 5.8	<b>&lt; 0.001</b>

*DT: Deceleration time; FAC: Fractional area change; LA: Left atrium; LAA: Left atrium area; LV: Left ventricular; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; PW: Posterior wall; RAA: Right atrium area; RV: Right ventricular; SPAP: Systolic pulmonary artery pressure; TAPSE: Tricuspid annular plane systolic excursion.*

\* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

MWD but not an independent predictor. In our study, we found that SPAP was an independent predictor for poor submaximal exercise capacity. In another study by Mirsaedi et al. SPAP, BNP and DLCO had correlation with 6 MWD (6). Both of these studies had no control group and did not use STE parameters.

We also demonstrated that subclinical cardiac dysfunction parameters regarding LVGLS, RVGLS, atrial conduit and reservoir functions were significantly lower in patients with sarcoidosis. Similarly,

Tigen et al. suggested that LV GLS, RV GLS and atrial conduit and reservoir functions were low in patients with sarcoidosis (7). Other studies showed that LV GLS and RV GLS were low in patients with sarcoidosis as well (8-10). However, these studies did not assess the effects of GLS on 6 MWD. In this study, we found that STE parameters were correlated with low 6 MWD but were not independent predictors.

Decreased LV GLS can be result of subclinical cardiac involvement or diastolic dysfunction. Previ-

**Table 4.** Comparison of two-dimensional speckle tracking echocardiography parameters between patients with sarcoidosis and controls\*

	Patients with sarcoidosis n = 56	Controls n = 26	P value
LV GLS (- %)	16.7 ± 4.1	22.8 ± 3.2	<0.001
LV GCS (- %)	19.1 ± 5.7	28.1 ± 4.4	<0.001
RV GLS (- %)	17.0 ± 5.2	23.4 ± 3.2	<0.001
LA reservoir function (%)	27.7 ± 11.0	41.1 ± 9.8	<0.001
LA conduit function (%)	14.2 ± 7.2	20.6 ± 6.0	<0.001
RA reservoir function (%)	27.4 ± 10.2	40.5 ± 8.4	<0.001
RA conduit function (%)	13.7 ± 6.5	20.3 ± 5.2	<0.001

*LA:* Left atrium; *LV GLS:* Left ventricular global longitudinal strain; *LV GCS:* LV global circumferential strain; *RA:* Right atrium; *RV GLS:* RV global longitudinal strain.

\* Numerical variables are displayed as mean ± standard deviation and categorical variables are displayed as percentages

**Table 5.** Linear regression analysis: Relationship between walking distance and significant correlated variables

Variables	Univariate analysis		Multivariate analysis*				
	R	P-value	95% CI		Standardised Coefficient	t-value	P-value
					Beta		
Age	-0.44	0.001	- 3.52	-0.08	-0.21	-2.10	<b>0.04</b>
BMI	-0.28	0.012	-5.71	0.83	-0.14	-1.48	0.14
FVC	0.26	0.018	-0.34	1.43	0.12	1.23	0.22
E/e' ratio	-0.30	0.006	-9.58	3.89	-0.08	-0.84	0.40
SPAP	-0.49	0.001	-4.7	-0.46	-0.28	-2.42	<b>0.02</b>
TAPSE	0.27	0.015	-4.24	4.22	-0.01	-0.01	0.99
LV GLS	-0.42	0.001	-7.93	1.55	-0.18	-1.34	0.18
RV GLS	-0.47	0.001	-6.03	2.98	-0.09	-0.68	0.50

\* Model R = 0.67, R<sup>2</sup> = 0.45

ous studies showed that patients with pulmonary sarcoidosis had LV diastolic dysfunction compared with controls (7, 26, 27). Accordingly, we found E/A ratio and E'-wave were low and NT-proBNP levels were high in patients with sarcoidosis compared with controls. Although E/E' ratio had correlation with low 6 MWD, it was not an independent predictor. RV GLS may be reduced as a result of RV involvement, secondary to LV dysfunction or comorbid lung disease resulting in elevated right-sided pressures. In our study, we didn't perform cardiac MRI (CMRI), positron emission tomography (PET) or endomyo-

cardial biopsy to evaluate primary RV involvement and the patients with sarcoidosis had no overt cardiac dysfunction (EF > 50%) and no significant differences compared with controls for EF, FVC or FEV1. We suggest that decreased TAPSE and FAC and increased RV wall thickness in patients with sarcoidosis can be a consequence of elevated right-sided pressures. Moreover, we demonstrated that higher SPAP in patients with sarcoidosis was an independent predictor for poor functional capacity. PHT is a feared complication in patients with sarcoidosis and early diagnosis is essential. However adequate tricus-

pid regurgitation velocity need to calculate SPAP is not always present. Based on our findings, 6 MWT can be an important screening tool for the development of PHT when SPAP is not reliably measured through TTE. Myocardial strain imaging parameters act as an early marker of cardiac dysfunction. This study demonstrated that decreased LV GLS and RV GLS levels were correlated with poor submaximal exercise capacity, although not an independent predictor. Future studies are needed to explore the prognostic role of 2D myocardial deformation imaging in patients with sarcoidosis.

### Study Limitations

Small sample cohort is an obvious limitation of the study due to low prevalence of sarcoidosis. Another limitation may be the lack of right heart catheterization data. Patients with mild PHT but no tricuspid regurgitation might have been missed using TTE. However, continuous measurement of pulse oximetry saturations during the 6 MWT in order to assess any desaturation could give more information for the exercise performance of the patients. Finally, comparison of STE findings with CMRI or PET findings in patients with subclinical cardiac involvement could be very demonstrative. Cost and availability of CMRI and PET is always a limiting factor however.

### CONCLUSIONS

Although subclinical cardiac dysfunction was readily detected using two-dimensional STE parameters, there were no independent correlations with submaximal exercise capacity assessed by 6 MWT. Older age and higher SPAP were independent predictors of poor submaximal exercise capacity in patients with sarcoidosis.

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