Assessment of right ventricular systolic and diastolic parameters in pulmonary sarcoidosis

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ABSTRACT

The clinical manifestations of cardiac involvement are seen in about 5% of patients with sarcoidosis; however, the incidence of cardiac involvement is higher in the autopsy series. About 14% of patients with pulmonary sarcoidosis (PS) without known cardiac involvement had diastolic dysfunction.

We aimed to determine the role of parameters of right ventricular (RV) systolic and diastolic function in patients with PS without evidence of cardiac symptoms. Our study population consisted of 28 patients with grades 1–4 PS and 24 healthy subjects. This study was a clinical prospective cohort study. RV end-diastolic area was found to be significantly higher in the PS group (p=0.032). RV fractional area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE) were shown to be statistically lower in the PS group as compared to the control group (p<0.001). However, pulmonary arterial systolic pressure was significantly higher in the PS group (p=0.003). The tricuspid E velocity and E/A ratio were found to be significantly lower in the PS group (p=0.025 and 0.009, respectively), while the tricuspid A velocity and myocardial performance index (MPI) were found to be significantly lower in the control group (p=0.034 and 0.007, respectively). Early detection of cardiac involvement in PS is crucial because of the increased morbidity and risk of sudden cardiac death. RV diastolic Doppler parameters, tissue Doppler MPI, RVFAC and TAPSE are practical and cheap techniques in the diagnosis of cardiac involvement in patients with PS. A thorough transthorasic echocardiographic examination including RV systolic and diastolic functions and tissue Doppler MPI should constitute the mainstay of initial management and follow-up in PS.

Significance of this study

What is already known about this subject?

Sarcoidosis and cardiac functions (especially the left ventricular diastolic functions) have been evaluated in some previous studies. A reversed E/A Doppler ratio together with a prolonged isovolumic relaxation time (IVRT) is among the most common echocardiographic patterns of diastolic dysfunction seen in early cardiac sarcoidosis. However, the relationship between sarcoidosis and right ventricular (RV) systolic and diastolic functions needs to be clarified.

What are the new findings?

RV diastolic Doppler parameters, tissue Doppler myocardial performance index, RV fractional area change, and tricuspid annular plane systolic excursion were found to be impaired in patients with sarcoidosis. These parameters are practical and cheap to be measured in the diagnosis of cardiac involvement in PS. The above RV echocardiographic measurements can be used as diagnostic tests and in follow-up of PS.

How might these results change the focus of research or clinical practice?

The early detection of cardiac involvement is very crucial because of the dismal prognosis of cardiac involvement among patients with sarcoidosis. Early detection and start of appropriate therapy can be lifesaving.

INTRODUCTION

The clinical manifestations of cardiac involvement are seen in about 5% of patients with sarcoidosis; however, the incidence of cardiac involvement is higher in the autopsy series.[1–4] It was reported that 19% of patients with extracardiac sarcoidosis had evidence of myocardial damage despite the fact that they had preserved left ventricular ejection fraction (LVEF).[5 6]

About 14% of patients with pulmonary sarcoidosis (PS) without known cardiac involvement had diastolic dysfunction.[1 7] A reversed E/A Doppler ratio together with a prolonged isovolumic relaxation time (IVRT) is among the most common echocardiographic patterns of diastolic dysfunction seen in early cardiac sarcoidosis (CS).[1 7] Although there are numerous articles about the relationship between left ventricular Doppler parameters and PS, the data are scant about right ventricular (RV) diastolic parameters such as tricuspid E, A, and E/A ratio in PS.

A non-invasive Doppler-derived myocardial performance index (MPI), which combines both systolic and diastolic function, was proposed by Tei *et al*.[8] It gives a better reflection of the global left or RV function than an

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isolated evaluation of either ejection or relaxation.[8–10] Increased MPI was reported to be a good prognostic index and independent predictor for cardiac death in various heart diseases.[10]

Tricuspid annular plane systolic excursion (TAPSE) is a practical measure of RV longitudinal function and was shown to be well correlated with techniques estimating RV global systolic function, such as radionuclide-derived RV ejection fraction (RVEF), two-dimensional (2D) RVFAC, and 2D RVEF.[11] Two-dimensional RV fractional area change (RVFAC) (%) is also used for estimation of RV systolic function.[11] There are few studies in the literature which have investigated the relationship between RV systolic function parameters and PS.

Either overt or obscured, cardiac involvement in sarcoidosis is associated with poor prognosis.[1] The regular monitoring of patients with PS in terms of cardiac symptoms, ECG, and echocardiography, and prompt initiation of anti-inflammatory therapy is crucial because of the increased risk of sudden death.[1] In this study, we aimed to determine the role of parameters of RV systolic and diastolic function in patients with PS without evidence of cardiac symptoms.

MATERIALS AND METHODS

Study population

Our study population consisted of 28 patients with grades 1–4 PS and 24 healthy subjects. This study was a clinical prospective cohort study. All patients were referred to our department by the outpatient clinic of the pulmonology unit of the medical faculty. All the patients had biopsy-proven disease identified by mediastinoscopy, thoracoscopy, or bronchoscopy. The grading of the disease was performed by using chest radiography according to the Scadding criteria[12] as follows: (1) bilateral hilar lymphadenopathy (BHL) with normal lung parenchyma; (2) BHL and parenchymal infiltration; (3) bilateral infiltration without BHL; and (4) pulmonary fibrosis (PF)/fibrocystic parenchymal involvement. The median disease duration was 21 months. There were 11 patients in grade 1, 15 patients in grade 2, 1 patient in grade 3, and 1 patient in grade 4. The spirometry of the patient group was performed by the pulmonology unit at admission and the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC, and the diffusing capacity of carbon monoxide (DLCO) were measured and recorded. Additionally, the peripheral oxygen saturations were measured by a pulse oximeter.

None of the study patients had cardiac symptoms or echocardiographic evidence of CS. Exclusion criteria were presence of coronary artery disease, hypertension, diabetes mellitus, renal failure, chronic obstructive pulmonary disease, heart failure, systolic LV dysfunction, moderate or severe valvular heart disease, atrial fibrillation, thyroid or parathyroid dysfunction, and connective tissue disease. The exclusion of arrhythmia was performed by ambulatory Holter monitoring. Our study was approved by the local ethics committee and informed consents were obtained from all of the study patients. The study was conducted in accordance with the Declaration of Helsinki.

Standard echocardiography

None of the patients were under medical therapy during echocardiography. All of the echocardiographic measurements were performed by two independent cardiologists blind to the clinical characteristics of the study population. Transthoracic echocardiography was performed using Vivid 7 Dimension (GE Vingmed Ultrasound AS N-3190, Horten, Norway) with a 2.5 MHz transducer. Patients were evaluated in the left lateral decubitus position after a rest of 5 min. The valve morphology and wall motion were assessed with M-mode and 2D echocardiography. The LVEF was measured by using the parasternal long-axis view. RV end-diastolic and end-systolic area (RVEDA and RVESA), RVFAC, TAPSE, and pulmonary arterial systolic pressure (PASP) were measured from an apical four-chamber view. RVEDA and RVESA were measured by determination of endocardial borders. RVFAC was determined by using apical four-chamber images by using the formula [(RVEDA–RVESA)/RVEDA×100]. TAPSE was measured by conventional M-mode echocardiography. PASP was calculated by the formula: 4×(tricuspid regurgitant jet velocity)^2+estimated right atrial pressure.

PW Doppler calculations of RV filling were made by screening the apical four chamber, while Doppler sampling was made parallel to the volume of RV long axis. The tricuspid early diastolic flow velocity (E wave), late diastolic flow velocity (A wave), and E/A ratio were recorded for evaluation. For MPI measurement, in an apical four-chamber screening, a 5 mm wide PW Doppler sampling of volume was placed on the intersection point between the RV free wall and the lateral tricuspid annulus. By letting the sample volume stay parallel to the wall axis, early diastolic annular velocity and late diastolic annular velocity flow speeds were recorded from the lateral tricuspid annulus. RV MPI is the ratio of the sum of RV IVRT and isovolumic contraction time divided by pulmonary ejection time. In other words, it was calculated as the difference between tricuspid regurgitation duration and ejection time (ET) divided by ET.

All of the calculations were repeated during the consecutive three heartbeats, and the mean values were calculated. All calculations followed the standards of the American Society of Echocardiography.[13]

Statistical analysis

Continuous variables are presented as mean±SD, while categorical variables are given as percentages. The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Statistical analysis of clinical data between the two groups consisted of unpaired t tests for parametric data, and the Mann-Whitney U test analysis for non-parametric data. Analyses were performed with PASW 18 (SPSS/IBM, Chicago, Illinois, USA) software, and a two-tailed p value <0.05 was considered statistically significant.

RESULTS

The baseline clinical, demographic, laboratory, and echocardiographic parameters were demonstrated in table 1. There was no statistically significant difference between the sarcoidosis and control groups in terms of age, gender, body mass index, smoking, total cholesterol, fasting glucose, systolic and diastolic blood pressures (SBP and DBP), heart rate, LVEF, and RVESA. The C reactive protein level was found to be significantly higher in the PS group ($p<0.001$). RVEDA was found to be significantly higher in

Table 1 The clinical, laboratory, and standard echocardiographic data of the patients with sarcoidosis and the control group

Parameters	Patients with sarcoidosis N=28	Control group N=24	p value
Age, years	40.22±11.92	37.57±5.20	0.640
Gender, F/M	15/13	13/11	0.435
BMI, kg/m^2	25.29±2.4	24.75±2.0	0.35
Smokers (n)	28	30	0.6
SBP, mm Hg	118.40±8.02	119.28±10.15	0.963
DBP, mm Hg	71.62±8.05	74.04±8.89	0.329
HR, bpm	81.92±8.23	77.09±5.62	0.124
Total cholesterol (mg/dL)	176.6±27.3	159.4±31.8	0.119
Fasting glucose (mg/dL)	90.4±9.9	86.1±11.8	0.098
CRP (mg/L)	1.7±0.4	0.4±0.1	<0.001
LVEF, %	64.14±2.55	65.80±2.40	0.260
Mitral E wave (cm/s)	78.6±16.0	90.0±12.8	0.01
Mitral A wave(cm/s)	72.2±20.1	62.3±9.0	0.04
Mitral DT (ms)	186.9±34.8	193.0±28.6	0.2
Mitral E/A ratio	1.07+0.32	1.2+0.36	0.03
RVEDA, cm^2	25.25±9.20	20.57±7.33	0.032
RVESA, cm^2	14.07±4.48	14.61±4.29	0.673
RVFAC, %	44.96±6.19	51.47±5.34	<0.001
TAPSE, cm	1.92±0.24	2.43±0.40	<0.001
PASP, mm Hg	32.54±5.84	24.36±3.78	0.003

A p value <0.05 was accepted as statistically significant.
BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; DT, deceleration time; F, female; HR, heart rate; LVEF, left ventricular ejection fraction; M, male; PASP, pulmonary arterial systolic pressure; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.

the PS group (p=0.032). RVFAC and TAPSE were shown to be statistically lower in the PS group as compared to the control group (p<0.001). However, PASP was significantly higher in the PS group (p=0.003). The mitral A wave velocity was significantly higher (p=0.04) and mitral E wave velocity and E/A ratio were significantly lower in patients with PS compared to the control group (p=0.01 and 0.03, respectively). The standard trans-tricuspid flow velocities and tissue Doppler velocities measured from the lateral tricuspid annulus were demonstrated in table 2. The tricuspid E velocity and E/A ratio were found to be significantly lower in the PS group (p=0.025 and 0.009, respectively), while the tricuspid A velocity and MPI were found to be significantly lower in the control group (p=0.034 and 0.007, respectively).

Table 2 The standard transtricuspid flow velocities and tissue Doppler velocities measured from the lateral tricuspid annulus

Parameters	Patients with sarcoidosis (n=28)	Control group (n=24)	p value
Tricuspid E (cm/s)	55.25±7.84	60.19±5.71	0.025
Tricuspid A (cm/s)	50.62±15.76	44.61±5.26	0.034
Tricuspid E/A ratio	1.18±0.27	1.36±0.16	0.009
MPI	0.48±0.08	0.43±0.04	0.007

A p value <0.05 was accepted as statistically significant.
MPI, myocardial performance index.

The mean spirometric data of the patients were as follows; FVC: 2.57±0.93 L (69±17%), FEV1:1.83±0.88 L (73±18%), FEV1/FVC: 79±7.8, DLCO: 68.5±16%. The mean oxygen saturation of the patients was 88±10% (table 3).

DISCUSSION

Our study showed that RVFAC, TAPSE, and MPI were significantly lower in patients with PS without clinical evidence of cardiac dysfunction. These findings are consistent with the findings of the study by Patel *et al*[5] in which 19% of patients with extracardiac sarcoidosis had evidence of myocardial damage despite having preserved LVEF. These findings raise the necessity of a comprehensive transthoracic echocardiographic examination in patients with PS who have no evidence of heart disease.

In the query of the previous literature, we did not find any study that showed the role of RVFAC in PS. Our study is the first to demonstrate the significant decrease in RVFAC in PS to date . RVFAC is a more reliable parameter and defined as the difference between end-diastolic and end-systolic area divided by the end-diastolic area multiplied by 100, from the apical four-chamber view.[14] RVFAC was reported to correlate with RVEF, which was measured by MRI with a lower reference value of 35%.[11 15]

TAPSE is another less-studied parameter in PS in the literature. As a practical measure of RV longitudinal function, it was shown to be well correlated with techniques estimating RV global systolic function, such as radionuclide-derived RVEF, 2D RVFAC, and 2D RVEF.[11] In the study by Keir *et al*,[16] after targeted therapy they have found statistically significant improvement in median TAPSE in patients with pulmonary hypertension (PH) with sarcoidosis. Our study showed lower TAPSE values in patients with PS compared to healthy controls. Regarding these findings, the use of TAPSE both in the diagnosis and follow-up of the therapy may be feasible.

There are numerous articles about the relationship between left ventricular Doppler parameters and PS;[7 10 17 18] however, the data regarding RV diastolic parameters such as tricuspid E, A, and E/A ratio in PS is limited. In our study, we examined both the conventional mitral and tricuspid Doppler parameters in patients with PS compared to healthy controls. The statistically significant difference in these parameters between groups in our study is important because in the previous studies there are

Table 3 The spirometric and oxygen saturation data of the PS group

	FVC (L)	FVC (%)	FEV1 (L)	FEV1 (%)	FEV1/ FVC	DLCO (%)	Oxygen saturation (%)
Mean	2.57	69	1.83	73	79	68.5	88
SD	0.93	17	0.88	18	7.8	16	10

DLCO, diffusing capacity of carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PS, pulmonary sarcoidosis.

conflicts regarding the mitral and tricuspid Doppler measurements. In the study by Kaya *et al*,[10] the tricuspid RV diameters, tricuspid diastolic velocities (E and A), E/A ratio, deceleration time (DT), and isovolumetric relaxation time were found to be similar in both the PS and control groups. In our study, both RV diastolic parameters and RV MPI were found to be impaired in the PS group compared to controls. In contrast to the study of Kaya *et al*,[10] we have also detected significant differences between groups in terms of LV diastolic parameters including E and A velocities and E/A ratio. Our results are more consistent with previous literature and indicate the importance of detailed echocardiographic examination in patients with PS.

We found significantly higher MPI values in patients with PS, a finding similar to that in previous reports. MPI is a non-invasive Doppler-derived parameter, and by combining both systolic and diastolic function, it gives a better reflection of the global LV or RV function than an isolated evaluation of either ejection or relaxation.[8–10] In a previous study, RV MPI was found to be impaired in patients with sarcoidosis, although systolic and diastolic function parameters were comparable in the patients and controls.[10] In our study, we have demonstrated a significant impairment in both RV diastolic parameters and MPI in patients with PS.

The diastolic dysfunction of the right ventricle may be a result of increased RV afterload due to PH.[10] PH was found to have a prevalence of 73.8% in advanced sarcoidosis and is a predictor of poor prognosis.[1 19] In a previous Japanese study, PH was found to be present in 5.7% of cases of CS.[1 20] In another study, sarcoidosis-related PH was found to be approximately 12% by Doppler echocardiography.[21] PH can be the result of decreased output due to poor left ventricular function or it can be seen in patients with PS with hypoxic vasoconstriction.[1 2] PH can also be caused by compression of the pulmonary vessels because of infiltration of intima and media by non-caseating granuloma and enlarged mediastinal lymph nodes.[1 22] In another study, it was reported that PH is mostly related to PF and CS causing diastolic dysfunction.[21] In our study, we have found that PASP, measured by echocardiography, was significantly higher in the PS group as compared to controls. This finding is consistent with previous studies. However, in our study, the mildly increased PASP might not have contributed alone to the RV diastolic dysfunction. Accordingly, we can propose that LV diastolic dysfunction together with mildly increased PASP can contribute to the RV diastolic impairment in our patients.

Although we could not perform a statistical analysis regarding pulmonary function test (PFT) because of the unequal distribution of the disease grade among the patients, the admission PFT data including FVC, FEV1, FEV1/FVC, and DLCO were found to be somewhat impaired.

Study limitations

The smaller sample size is the major limitation of the study. Since it was a cross-sectional study, there was no long-term follow-up of cardiovascular morbidity and mortality.The lack of confirmation of these parameters by another imaging modality such as MRI or radionuclide scintigraphy is another limitation. Despite the smaller sample size, our study showed that RVFAC, MPI, and TAPSE can be helpful in patients with sarcoidosis showing subclinical RV dysfunction before overt dysfunction occurs.

CONCLUSION

Early detection of cardiac involvement in PS is crucial because of increased morbidity and risk of sudden cardiac death.[23–25] RV diastolic Doppler parameters, tissue Doppler MPI, RVFAC, and TAPSE are practical and cheap techniques in the diagnosis of cardiac involvement in patients with PS. A thorough transthoracic echocardiographic examination including RV systolic and diastolic functions and tissue Doppler MPI should constitute the mainstay of initial management and follow-up in PS. The role of these parameters in PS needs to be supported in further prospective studies of larger sample size.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Local ethics committee of Erzurum Training and Research Hospital.

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