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Cardiac Image

Impaired Left Ventricular Diastolic Functions and Thickened Epicardial Adipose Tissue in Rheumatoid Arthritis Patients is Correlated with DAS-28 Score

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease that is known to be associated with high cardiovascular (CV) morbidity and mortality. In this study, we aimed to demonstrate whether RA disease activity reflected with disease activity score-28 (DAS-28) had an impact on left ventricular diastolic functions and epicardial adipose tissue (EAT) thickness in RA patients with no traditional CV risk factors.

Methods: In this retrospective study, 41 patients newly diagnosed with RA were included. In addition to medical history, detailed physical examination findings and laboratory tests, left ventricular systolic and diastolic functions, chamber dimensions, and EAT thickness were evaluated with transthoracic echocardiography in the study population.

Results: This study included 41 subjects with a median age of 45 years (38.00-55.50), of which 29.27% were male. In the binomial logistic regression analysis, DAS-28 score was found to be an independent associate of diastolic dysfunction, Additionally, DAS-28 was found to be independently associated with EAT thickness.

Conclusions: Patients with high DAS-28 score should be evaluated thoroughly for CV disease, and patients should undergo advanced diagnostic studies as required and receive appropriate treatment.

Key Words: Echocardiography • Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease. Autopsies have revealed a high incidence of pericardial, myocardial, and endocardial involvement in RA patients.[1] Although known to be associated with high cardiovascular (CV) morbidity and mortality,[2] it remains unclear whether traditional CV risk factors or inflammation and autoimmunity associated with the disease contribute to CV risk in RA patients.[2]

Left ventricular diastolic dysfunction (LVDD) may be detected prior to overt CV disease symptoms in a wide variety of patients with chronic inflammatory diseases.[3,4] Previous studies have reported that impaired left ventricular diastolic parameters[5,6] are predictors of adverse cardiovascular adverse events. Furthermore, epicardial adipose tissue (EAT) thickness has recently emerged as a new marker of cardiometabolic risk.[7-9] In this study, we aimed to demonstrate whether RA disease activity reflected with disease activity score-28 (DAS-28) had an impact on left ventricular diastolic functions and EAT thickness in RA patients with no traditional CV risk factors.

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MATERIALS AND METHODS

Study population

In this retrospective study, we included 41 patients newly diagnosed with RA, with a disease activity score ≥ 6/10 based on the current RA diagnosis criteria from the American College of Rheumatology and the European League against Rheumatism.[10] Patients were excluded if they had a previous history of ischemic heart disease, atrial fibrillation/flutter, cerebrovascular disease, hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia, family history of premature coronary artery disease, or smoking (Figure 1).

This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

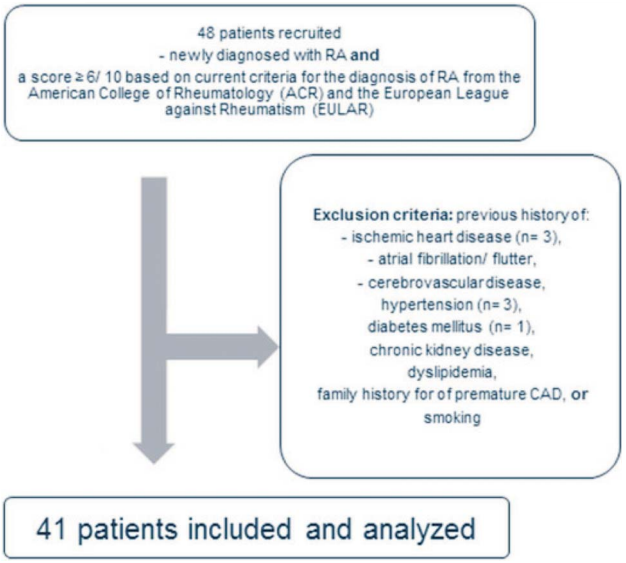

Figure 1. *Flow chart of study population selection. CAD, coronary artery disease; RA, rheumatoid arthritis.*

Study protocol

Medical history and detailed physical examination findings were recorded for all patients. The disease activity score-28 (DAS-28) was determined by total joint count (28 joints).[11] In addition to routine complete blood cell count and biochemistry tests, left ventricular systolic and diastolic functions, chamber dimensions, and EAT thickness were evaluated with transthoracic echocardiography (TTE) in the study population.

Transthoracic echocardiography

All patients underwent a comprehensive TTE examination during sinus rhythm, utilizing a Philips Epiq 7® Ultrasound Machine with a 3.6 MHz.probe. Echocardiographic measurements were acquired from three consecutive beats.

Left ventricular ejection fraction was assessed using Simpson's method. Left atrial diameter was obtained in the parasternal long axis view. Doppler analysis of mitral inflow and tissue Doppler imaging were recorded to assess left ventricular diastolic dysfunction. Mitral flow E and A peak velocities, E/A ratio, and deceleration time (DT) of mitral early velocity were measured from the apical four chamber (A4C) view, with the sample volume placed at the level of the mitral leaflet tips. Pulsed tissue Doppler imaging measurements of mitral annulus motion were performed in the A4C view with sample volume placed at the septal and lateral aspects of the mitral annulus. Early (E_m) and late (A_m) diastolic mitral annular peak velocities were measured, and then E/E_m and E_m/A_m ratios were calculated. Isovolumic relaxation time (IVRT) was measured during Doppler imaging of the LV outflow tract. Diastolic dysfunction was defined according to EAE/ASE recommendations.[12] Patients with normal left ventricular (LV) systolic functions were included. In this patient group, the E/E_m ratio was calculated to estimate LV filling pressure, and an average ratio ≤ 8 identified patients with normal LV filling pressure. Additionally, septal E_m, lateral E_m, and left atrial volume index (LAVI) were used to determine diastolic dysfunction. Patients with septal $E_m \geq 8$ cm/s, lateral $E_m \geq 10$ cm/s and LAVI < 34 ml/m^2 showed normal diastolic functions; if not, they were confirmed to have diastolic dysfunction.

Epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium. EAT thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles on standard parasternal views. Maximum EAT thickness was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. The average value of three cardiac cycles from each echocardiographic view was taken into account.

The transthoracic echocardiographic parameters

were evaluated by a single blinded observer. Intra-observer variability testing for repeated EAT thickness measurements from 20 subjects revealed an intra-class correlation coefficient of 0.964 ($p < 0.001$).

Statistical analysis

Normally distributed parameters were presented as mean ± standard deviation, and skewed parameters were expressed asmedian (interquartile range defined as 25-75th percentiles). Descriptive data were presented as frequencies (number and percentage) and compared using chi-square test. Univariate analyses were performed on continuous variables with the use of the independent Student's t-test for normally distributed variables, and the Mann-Whitney U test for non-normally distributed data. Spearman's correlation analysis was used to demonstrate the correlation between DAS-28 score and baseline characteristics. Linear regression analysis was used for identifying factors that were independently correlated with E/E_m and EAT thickness. Binomial regression analysis was performed to determine factors independenty associated with diastolic dysfunction. Statistical analyses were performed using SPSS statistical software (version 21.0; SPSS Inc., Chicago, Illinois, USA). A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

In this study, 41 subjects with a median age of 45 years (38.00-55.50) were included, and 29.27% were male. Of those patients, 12 had diastolic dysfunction (Table 1); other baseline characteristics of the study population are also shown in Table 1.

Independent samples t-test showed that DAS-28 score was significantly higher in patients with diastolic dysfunction [5.39 (3.42-6.54) vs. 4.23 (1.88-6.30), $p = 0.005$]. In Spearman's correlation analysis, DAS-28 score was found to be positively correlated with EAT thickness ($r = 0.365$, $p = 0.02$). In the binomial logistic regression analysis, DAS-28 score was found to be an independent associate of diastolic dysfunction (OR: 2.556, 95% CI: 1.266-5.160, $p = 0.009$) (Table 2). In the linear regression analysis, DAS-28 was found to be independently associated with EAT thickness (Table 3).

Table 1. Baseline characteristics of the study population (n = 41)

Parameters	Patients with rheumatoid arthritis (n = 41)
Age (years)	45.00 (38.00-55.50)
Gender: male (%)	12 (29.27)
Body mass index (kg/m^2)	28.42 ± 7.50
Left ventricular ejection fraction (%)	62.68 ± 4.10
Left ventricular end-diastolic diameter (mm)	45.85 ± 4.61
Left atrial diameter (mm)	36.90 ± 3.81
Mitral flow E (cm/s)	72.00 (62.43-89.08)
Mitral flow A (cm/s)	85.00 (72.75-95.00)
Mitral flow E/A	0.89 (0.69-1.07)
Deceleration time of flow velocity in early diastole (ms)	201.00 (168.00-259.50)
Isovolumetric relaxation time (ms)	86.00 (67.00-95.00)
Mitral annulus E_m (cm/s)	10.69 (8.16-12.36)
Mitral annulus A_m (cm/s)	11.00 (9.13-13.07)
Mitral annulus E_m/A_m	0.93 (0.75-1.16)
Mitral annulus E/E_m	6.68 (5.65-8.85)
Epicardial adipose tissue thickness (cm)	0.39 (0.32-0.48)
Disease activity score-28	4.32 (3.22-5.44)
C-reactive protein (mg/L)	10.30 (3.33-32.55)
Erythrocyte sedimentation rate (mm)	37.00 (16.00-50.50)

A, late diastolic flow velocity; A_m, mitral annular late diastolic velocity; E, early diastolic flow velocity; E_m, mitral annular early diastolic velocity.

Table 2. Binomial regression analysis for identifying independent associates of diastolic dysfunction in the patient group (n = 41)

Model	OR	95% confidence interval for B		p value	OR	95% confidence interval for B		p value
		Lower bound	Upper bound			Lower bound	Upper bound	
Body mass index (kg/m^2)	1.095	0.988	1.214	0.08	1.123	0.988	1.278	0.08
Disease activity score-28	2.440	1.215	4.898	0.01*	2.556	1.266	5.160	0.009*

OR, odds ratio; SD, standard deviation.
a Dependent variable: diastolic dysfunction. * Denotes statistical significance.

Table 3. Linear regression analysis for identifying independent associates of epicardial adipose tissue thickness in the patient group (n = 41)

Model	B ± SD	95% confidence interval for B		p value	B ± SD	95% confidence interval for B		p value
		Lower bound	Upper bound			Lower bound	Upper bound	
Age (years)	0.241 ± 0.114	0.010	0.471	0.04*	0.216 ± 0.109	-0.005	0.437	0.06
Disease activity score-28	2.417 ± 1.143	0.104	4.730	0.04*	2.184 ± 1.004	0.148	4.219	0.04*
Erythrocyte sedimentation rate (mm)	0.845 ± 0.662	-0.494	2.184	0.21	-	-	-	-

SD, standard deviation.
a Dependent variable: epicardial adipose tissue thickness (mm). * Denotes statistical significance.

DISCUSSION

Findings of our study demonstrated that patients with RA had impaired left ventricular functions and increased EAT thickness correlated with DAS-28, despite being free from traditional cardiovascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, smoking, or family history for coronary artery disease.

Rheumatoid arthritis and echocardiographic parameters

LVDD in RA has been attributed to common structural abnormalities such as hypertrophy or interstitial fibrosis, and impaired myocyte relaxation resulting from ischemia.[13] Vasculitis,[14] nodular granulomatous lesions,[1] myocarditis[15] and arteritis[16] have also been reported in patients with RA. Amyloidosis may also contribute to diastolic dysfunction in this disease.[17]

Previous studies have shown that LVDD existed in patients with RA without clinically prominent cardiac disease. E and E/A ratio were found to decrease, and IVRT and DT values were found to increase in patients with RA compared to the control group.[18-27] Of the tissue doppler imaging parameters, E_m and E_m/A_m ratios were found to be lower in RA patients than in the control group.[23] E/E_m ratio was found to be significantly higher in RA patients compared to healthy patients in a more recent study.[20] Only one study has reported similar E and A velocities, E/A ratio, and pulmonary venous Doppler parameters in RA patients and control group;[28] however DT, IVRT, A_m, E_m/ A_m, and E/E_m parameters in RA showed statistically significant differences in RA patients in the same study.[28] Our study reported that diastolic dysfunction was an independent associate of diastolic dysfunction. Although a previous study had reported no correlation between diastolic dysfunction and DAS-28 score,[29] this may be due to the fact that the former study included patients who were already diagnosed with RA and received treatment.

Rheumatoid arthritis and EAT

Several studies have demonstrated that EAT thickness was increased in patients with RA. A cross-sectional study conducted with a cohort of 34 female RA patients and 16 controls matched for age and body mass index have shown that female patients with RA had a greater EAT thickness than those without RA.[30] Another cross-sectional study that included 76 patients with RA and 50 age and gender-matched controls has reported that EAT thickness was greater in patients

with RA.[20] A recent cross-sectional study has demonstrated in 90 RA patients and 59 age- and gender-matched control subjects that patients with RA had thicker EAT.[31] Our study has shown that EAT thickness in RA patients was positively correlated with DAS-28. However, despite a significant correlation between EAT thickness and hs-CRP plasma concentration; other studies have failed to demonstrate a correlation between EAT thickness and DAS-28.[29-31]

The higher visceral adiposity reflected by increased EAT thickness has been suggested to be related to the use of glucocorticoids by RA patients, since they are known to promote deposition of visceral fat.[32] The so-called "cachectic obesity" in RA has been characterized by a loss of muscle tissue and significant fat gain,[33] therefore, EAT thickness has been proposed to constitute a better marker of visceral adiposity when compared with body mass index andwaist circumference.

Higher DAS-28 scores indicate increased inflammatory activity in rheumatoid arthritis patients. Since pro-inflammatory status was linked with LVDD and increased EAT thickness in previous studies, although not presenting with cardiovascular disease (CVD) or traditional CV risk factors, RA patients with higher DAS-28 scores may be expected to have incident CVD, owing to the fact that both LVDD and EAT thickness are related with incident CVD or adverse CV events.

CONCLUSIONS

Findings of the current study suggest that patients with high DAS-28 score should be evaluated thoroughly for CV disease. This is because left ventricular diastolic dysfunction and increased epicardial adipose tissue thickness, both of which are correlated to DAS-28 score, are regarded as markers of cardiovascular risk. Newly diagnosed rheumatoid arthritis patients with high DAS-28 scores should undergo advanced diagnostic studies if required and receive appropriate treatment.

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All authors declare no conflict of interest.

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