Arch Rheumatol 2024;39(2):303-311
doi: 10.46497/ArchRheumatol.2024.10274

ORIGINAL ARTICLE

The importance of speckle tracking echocardiography in the evaluation of cardiac functions in patients with rheumatoid arthritis

Müşerref Ebik[1], Nurettin Taştekin[1], Muhammet Gürdoğan[2], Mustafa Ebik[2], Murat Birtane[1], Hakan Emmungil[3], Barış Yılmazer[3], Necdet Süt[4]

[1]*Department of Physical Medicine and Rehabilitation, Trakya University Faculty of Medicine, Edirne, Türkiye*
[2]*Department of Cardiology, Trakya University Faculty of Medicine, Edirne, Türkiye*
[3]*Department of Internal Medicine, Division of Rheumatology, Division of Rheumatology, Trakya University Faculty of Medicine, Edirne, Türkiye*
[4]*Department of Biostatistics, Trakya University Faculty of Medicine, Edirne, Türkiye*

Correspondence: Müşerref Ebik, MD.
E-mail: museref-70@hotmail.com

Received: April 07, 2023
Accepted: November 13, 2023
Published online: February 06, 2024

Citation: Ebik M, Taştekin N, Gürdoğan M, Ebik M, Birtane M, Emmungil H, et al. The importance of speckle tracking echocardiography in the evaluation of cardiac functions in patients with rheumatoid arthritis. Arch Rheumatol 2024;39(2):303-311. doi: 10.46497/ArchRheumatol.2024.10274.

ABSTRACT

Objectives: In this study, we aimed to analyze the layer-specific strain values obtained by speckle tracking echocardiography (STE) method in the determination of subclinical cardiac dysfunction in rheumatoid arthritis (RA) patients.

Patients and methods: Between February 2019 and October 2019, a total of 63 female RA patients (mean age: 51.82±6.07 years; range, 40 and 65 years) who had a confirmed diagnosis were included. Thirty-one age-matched female healthy individuals (mean age: 50.71±5.37 years; range, 40 and 65 years) were selected as the control group. The patients were divided into three groups according to the duration of disease as <5 years, 5-10 years and >10 years. The Disease Activity Score in 28 joint - C-reactive protein (CRP) was used to determine disease activation. The standard assessment included complete serum CRP, anti-cyclic citrullinated peptide, rheumatoid factor, N-terminal pro B-type natriuretic peptide (NT-proBNP), and homocysteine. Global longitudinal strain (GLS) analysis was performed with STE.

Results: The NT-proBNP values were found to be higher in RA patients compared to the control group (p=0.044). In terms of conventional echocardiographic parameters, a significant difference between E/A and E/E' ratios was observed (p<0.001 and p=0.015). Endocardium, transmural, and epicardium GLS values obtained by STE were found to be lower in RA patients (p<0.05). The left ventricular (LV) GLS values worsened, as the duration of disease increased (p<0.05). There was a significant correlation between RA disease activity and LV GLS values, showing that increasing levels of disease activity was associated with worse LV GLS (r=0.583, p<0.01 and r=0.681, p<0.01 and r=0.689, p<0.01 for endocardium, transmural and epicardium, respectively).

Conclusion: Our study results suggest that the layer-specific GLS values obtained by STE decrease in RA patients.

Keywords: Layer specific global longitudinal strain, rheumatoid arthritis, speckle tracking echocardiography.

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory, progressive and systemic disease that includes joint arthritis[1] It is known that the incidence of many cardiovascular diseases, most frequently atherosclerosis and heart failure, are increased in RA patients causing significant mortality and morbidity.[2,3]

Primary left ventricular (LV) systolic dysfunction is more common in patients with RA compared to the general population. It is an early, silent cardiac event that occurs before the clinical signs of RA appears and is an important cause of heart failure with preserved ejection fraction (EF).[4]

In general, EF is measured with conventional two-dimensional (2D) echocardiography parameters such as M-mode and Simpson's method, and LV wall movements are evaluated. However, these parameters have important limitations. Therefore, strain echocardiography analysis is performed with the 2D point tracking ("speckle tracking") method which is not affected by the increase in the angle between the ultrasound wave and myocardial movement and has been used in the evaluation of the systolic functions of the ventricles in recent years.

In the present study, we aimed to analyze the layer-specific (endocardial, transmural and epicardial) strain values obtained by speckle tracking echocardiography (STE) to determine subclinical cardiac dysfunction in RA patients and to investigate the possible correlation between Disease Activity Score in 28 joints (DAS28), disease duration, and anti-cyclic citrullinated peptide (anti-CCP) titers with strain values.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at Departments of Physical Medicine and Rehabilitation and Internal Diseases Rheumatology Department of Trakya University Faculty of Medicine between February 2019 and October 2019.[5] A total of 63 female RA patients (mean age: 51,82±6,07 years; range, 40 and 65 years) who had a confirmed diagnosis according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria were included. The patients were grouped according to their disease duration as <5 years, 5-10 years, and >10 years. Male patients and those having diabetes mellitus, hypertension, atrial fibrillation, coronary artery disease, ischemic cerebrovascular disease, structural-congenital heart disease, heart valve disease, and history of smoking were excluded from the study. Thirty-one age-matched female healthy individuals (mean age: 50.71±5.37 years; range, 40 and 65 years) were selected as the control group.

The Short Form-36 (SF-36) scale was administered to both groups to evaluate the quality of life. The DAS28, which is based on the evaluation of 28 joints calculated by tender and swollen joint count, C-reactive protein (CRP) value, and the patient global assessment of disease activity on the Visual Analog Scale (VAS) was used to determine RA inflammatory activity.[6] The scores lower than 3.2 were considered as low disease activity, between 3.2 and 5.1 as moderate disease activity, and higher than 5.1 as high disease activity.

Laboratory tests

Blood samples were taken from all participants after overnight fasting. The CRP, anti-CCP, rheumatoid factor (RF), N-terminal pro B-type natriuretic peptide (NT-proBNP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), and homocysteine levels were measured. Anti-CCP levels were measured in U/mL by spectrophotometric measurement via the Beckman Coulter AU5800 device (Beckman Coulter, Inc., CA, USA). The RF levels were measured in IU/mL by nephelometric method via the Siemens BN2 device (Siemens Healthcare GmbH, Forchheim, Germany). The NT-proBNP levels were measured in pg/mL by nephelometric method via the VIDAS® 3 bioMérieux device (bioMerieux Inc., Durham, USA) and homocysteine levels were measured in µmoL/mL by immunoassay method via the Siemens IMMULITE 2000 device (Siemens Healthcare GmbH, Forchheim, Germany).

Echocardiography

Echocardiographic images of all groups were acquired using the Vivid S70 system (GE Healthcare, Horton, Norway) and transferred to the EchoPAC workstation. The M-mode, 2D, pulsed-wave (PW) Doppler, continuous wave (CW) Doppler, and color Doppler measurements were made according to the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines.[7] All standard measurements were obtained from the parasternal long and short axes, with apical two- and four-chamber views. The EF was calculated by using the modified biplane Simpson's rule. The LV diastolic and systolic dimensions, ventricular septum and posterior wall thickness, and left atrial dimension were obtained from parasternal long-axis images using M-mode. The mitral inflow velocities were recorded from the apical four-chamber view by PW Doppler with the sample volume placed at the level of the mitral valve tips. Early (E) and late (A) peak mitral and tricuspid inflow velocities, isovolumetric relaxation time (IVRT), deceleration time (DT) were obtained and the E/A ratio was calculated. An E/A ratio of ≥1.0 was defined as normal and <1.0 was equivalent for diastolic dysfunction. Mitral annular velocities were measured by Doppler tissue imaging using the PW mode. Early diastolic mitral annular (E´), late diastolic (A´),

systolic velocities (S´) and E/E´ ratio of the mitral annulus were measured from the apical four-chamber view.

It is a relatively new advanced echocardiographic examination method that allows evaluating the strains of the endocardial, transmural and epicardial layers using the 2D STE method.[8] Layer-specific strain values obtained with STE enable the detection of LV systolic functions in the subclinical period compared to traditional 2D echocardiographic methods.[8,9] The 2D STE analysis was performed by an experienced cardiologist, blind to the patient data, according to the guidelines from the recorded 2D gray-scale images.[8] The EchoPAC software was recorded without clinical knowledge of the patients as a cine-loop and studied from the apical view (apical two-chamber, four-chamber, and apical long-axis views) from three-beat recordings at 50 to 80 frames/sec. A 17-segment bull's eye view was created after processing all three apical images. From this view, the endocardial, epicardial, and mid-myocardial (transmural) longitudinal strain values of the LV were calculated automatically by the EchoPAC software.[9]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The conformity of the quantitative data to the normal distribution was examined using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) or Kruskal-Wallis tests were used to compare the quantitative values among the four groups. The Mann-Whitney U test was used to compare the values of both patients and controls. The chi-square test was used to compare categorical data. The Pearson or Spearman correlation analysis was used in the analysis of the relations between the variables, taking into account the distribution characteristics of the data. A *p* value of <0.05 was considered statistically significant.

RESULTS

There were 63 RA patients with unknown cardiac conditions in this study. Those with a disease duration of <5 years were considered as the first group, between 5-10 years as the second group, and >10 years as the third group. No significant difference was observed among the three groups of RA patients and the control group in terms of mean age and body mass index (BMI) (50.90±6.73 *vs.* 50.57±4.43 *vs.* 54.00±6.49 *vs.* 50.71±5.37, p>0.05) (Table 1).

Cardiovascular disease risk factors, such as blood pressure, levels of TC, HDL-C, LDL-C, and TG were comparable between RA patients and controls. There was no significant difference between the groups in terms of treatment

Table 1. Baseline demographic and clinical characteristics of the studied groups

	First group <5 year RA	Second group 5-10 year RA	Third group >10 year RA	Control group	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p*
Age (year)	50.90±6.73	50.57±4.43	54.00±6.49	50.71±5.37	0.161
Body mass index (kg/m²)	28.81±5.18	29.04±4.33	27.84±4.87	26.46±3.85	0.155
Systolic blood pressure (mmHg)	111.19±13.41	107.14±11.90	11.90±16.32	108.71±12.04	0.732
Diastolic blood pressure (mmHg)	74.52±7.31	72.62±9.44	76.19±11.61	71.29±6.70	0.324
Total serum cholesterol (mg/dL)	204.43±38.74	208.71±34.12	205.81±39.53	223.13±37.90	0.240
HDL-C (mg/dL)	53.76±10.50	52.43±9.43	54.66±10.50	54.48±11.91	0.898
NT-proBNP (pg/mL)	88.14±67.61	93.28±61.54	130.67±101.28	68.97±58.28	0.164
Homocysteine (µmol/mL)	10.85±4.26	10.30±3.65	10.86±4.67	9.45±3.00	0.694

RA: Rheumatoid arthritis; SD: Standard deviation; HDL-C: High-density lipoprotein cholesterol; NT-proBNP: N-terminal pro B-type natriuretic peptide.

Table 2. Comparison of layer-specific 2D GLS values of patient and control groups

	First group <5 year	Second group 5-10 year	Third group >10 year	Control group	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p*
GLS endocardium	–23.98±1.84	–23.29±1.59	–21.71±1.93	–24.95±0.73	[+]0.000 [β]0.000 [ɲ]0.001
GLS transmural	–21.78±1.71	–21.20±1.66	–19.85±1.50	–22.98±1.17	[+]0.001 [δ]0.020 [†]0.017 [ɲ]0.001 [β]0.000
GLS epicardium	–20.05±2.02	–19.23±1.77	–17.98±1.38	-20.83±0.70	[δ]0.023 [β]0.000 [+]0.000 [ɲ]0.001

SD: Standard deviation; GLS: Global longitudinal strain; x: First-second; &: Second-third; †: Third-control; +: First-third; †: First-control; [ɲ]: Second-control.

regimens (p>0.05). None of the patients had high disease activity (Table 1).

The LV global longitudinal strain (GLS) values worsened, as the duration of disease increased (p<0.05). There was a significant correlation between RA disease activity and LV GLS values, showing that increasing levels of disease activity was associated with worse LV GLS (r=0.583, p<0.01 and r=0.681, p<0.01 and r=0.689, p<0.01 for endocardium, transmural and epicardium, respectively) (Table 2).

Table 3. The LV echocardiographic characteristics of the studied groups

	RA patients (n=63)	Healthy controls (n=31)	
	Mean±SD	Mean±SD	*p*
Left atrium (mm)	33.35±3.69	31.90±2.79	0.061
LV mass index (g/m^2)	83.33±18.03	75.84±18.46	0.024
IVRT (m/sec)	74.56±5.77	71.52±6.02	0.024
EF (%)	62.19±4.73	62.00±5.03	0.977
Mitral E (cm/sec)	0.78±0.17	0.80±0.14	0.405
Mitral A (cm/sec)	0.82±0.15	0.72±0.12	0.001
Mitral E/A (cm/sec)	0.95±0.21	1.14±0.20	<0.001
Mitral E` (cm/sec)	0.11±0.03	0.12±0.02	0.065
Mitral A` (cm/sec)	0.11±0.02	0.10±0.02	0.011
Mitral E/E` (cm/sec)	7.62±1.73	6.76±1.64	0.015

LV: Left ventricular; RA: Rheumatoid arthritis; SD: Standard deviation; IVRT: Isovolumic relaxation time; EF: Ejection fraction; E: Peak flow velocity during the early rapid filling phase; A: Peak flow velocity during atrial contraction; E/ E`: The ratio of early flow velocity to the early annular velocity.

The NT-proBNP values of RA patients were found to be higher than the control group (104.03±79.81 pg/mL *vs.* 68.97±58 pg/mL, p=0.044) and homocysteine levels were found to be similar (p>0.05). The NT-proBNP levels were positively correlated with disease activity, but this correlation was not statistically significant (p>0.05). The NT-proBNP levels were found to be 88.14±67.61 pg/mL, 93.28±61.54 pg/mL, and 130.67±101.28 pg/mL in first, second, and third groups of RA patients, respectively (Table 3).

The LV GLS was significantly correlated with anti-CCP and RF titers with higher values were associated with worse LV GLS (r=0.467, p<0.01 and r=0.509, p<0.01 and r=0.551, p<0.01 are given for the endocardium, transmural and epicardium, respectively). In terms of the characteristics and markers, no significant correlation was found between LV GLS and the NTproBNP levels (r=0.070, p=0.585 and r=0.149, p=0.284 and r=0.078, p=0.546 for endocardium, transmural and epicardium, respectively) (Table 3).

Considering conventional echocardiographic parameters, EF of RA patients and control group was found to be similar (p>0.05). As related to diastolic dysfunction, RA patients showed lower E/A and higher E/E´ ratio (0.95±0.21 *vs.* 1.14±0.20, p<0.001, 7.62±1.73 *vs.* 6.76±1.64,

Table 4. Correlation between clinical variables and parameters of left ventricular functions

	GLS endocardium		GLS transmural		GLS epicardium	
	r	*p*	r	*p*	r	*p*
DAS28	0.467	0.000	0.509	0.000	0.551	0.000
NT-proBNP	0.070	0.585	0.149	0.284	0.078	0.546
Ejection fraction	-0.142	0.267	-0.134	0.234	-0.064	0.618
Mitral E/E'	-0.042	0.745	-0.074	0.566	-0.068	0.595
IVRT	-0.184	0.148	-0.151	0.238	-0.121	0.347
Anti-CCP	0.583	0.000	0.687	0.000	0.689	0.000
RF	0.424	0.000	0.479	0.000	0.511	0.000

GLS: Global longitudinal strain; DAS28: Disease Activity Score in 28 Joints; NT-proBNP: N-terminal pro B-type natriuretic peptide; E/ E': The ratio of early flow velocity to the early annular velocity; IVRT: Isovolumic relaxation time; Anti-CCP: Anti cyclic citrullinated peptide; RF: Rheumatoid factor.

p=0.015). The E/A ratio decreased as the disease duration increased (p<0.05). The IVRT was prolonged in RA patients compared to the controls (74.56±5.77 *vs.* 71.52±6.02, p=0.024). When the groups were compared in terms of endocardial, transmural and epicardial GLS values obtained by STE, endocardium, transmural and epicardial GLS values were found to be lower in RA patients (p<0.05) (Table 4).

Echocardiographic dysfunction parameters showed high correlation with physical health and pain related SF-36 subscale scores (SF-36-PF, SF-36-RP, and SF-36-BP).

DISCUSSION

The main finding of this study is that GLS measured by LV STE decreased, as the disease duration increased in RA patients with normal EF compared to the normal population. In addition, a positive correlation was observed between the degree of GLS reduction of the LV and DAS28 score, anti-CCP and RF titers.

Chronic immunity activation and inflammatory mechanisms triggered by the overactivity of cytokines play a role in the progression of cardiomyocyte apoptosis, myocardial fibrosis, ventricular dysfunction and consequently heart failure. In a recent study, abnormal E/A ratio was observed in older RA patients with longer disease duration and high inflammatory and immunological parameters.[2,10]

In another study in 78 patients with RA, the importance of the decrease in GLS values was emphasized and this was correlated with DAS28-CRP, in line with the findings of this study, although there was no significant decrease in patients' EF values (–18.9±3.1% *vs.* –20.6±3.5%, p<0.01).[11]

In the study conducted by Biskup *et al.*[2] examining the cardiac functions of 70 RA patients with low disease activity, it was shown that patients with abnormal E/A ratio had higher inflammatory and immunological parameters along with longer disease duration and age.

In a study examining LV diastolic functions in RA patients, patients had decreased mitral E/A ratio and prolonged IVRT values. In this study, DAS28 disease activity index was found to be the only independent predictor of LV diastolic dysfunction, and the severity of disease activity was an important factor for heart failure. When LV diastolic function parameters were assessed with conventional and tissue Doppler echocardiography, mitral E/E' ratio was higher in RA patients compared to the control group and the mitral E/A ratio was lower in RA patients. This finding indicates that LV diastolic filling pressure increases and diastolic functions are altered in RA patients. Similarly, it has been reported in previous studies that the presence of RA is a predisposing factor for diastolic dysfunction. In the aforementioned study, it was further revealed that not only the presence of RA, but also the degree of diastolic dysfunction

was correlated with increasing RA disease duration.[12]

In the study conducted by Naseem et al.[13] which evaluated the correlation between disease activity scores and ventricular GLS values, worse LV GLS values were observed with increasing disease activity levels. The distinguishing feature of the present study is that not only the LV GLS values, but also the GLS values of endocardial, transmural and myocardial layers were analyzed separately. When the strain values of all three layers were compared with DAS28-CRP separately, increased disease activity was shown to be associated with lower strain values.

In a study investigating the difference in cardiovascular changes before and after the five-year follow-up period, mitral A velocity increased and mitral E/A velocity decreased by time. The authors showed that the rates of change in LV diastolic function over five years were significantly higher. In the present study, the fact that RA patients with disease duration of >10 years had decreased mitral E/A and increased mitral E/E' velocity, compared to the RA patients with disease duration of <5 years underlined the importance of the duration of disease on the progression of heart failure and that the disease should not be left untreated.[14]

Benacka et al.[15] showed that LV mass index was higher and EF was lower in RA patients in standard echocardiographic examination and also reported that IVRT was prolonged and mitral E/E' ratio increased. They found NT-proBNP levels to be higher in RA patients and did not detect a significant correlation between NT-proBNP level and EF, IVRT, E/E'. In the present study, RA patients had an increase in the LV mass index, a prolonged IVRT, an increase in the mitral E/E' ratio, and a higher NT-proBNP levels. Similarly, the EF of the RA group was detected lower than that of the control group; however, this difference did not reach statistical significance. In addition, the fact that the strain values in the endocardium, transmural and epicardium layers were found to be lower in RA patients with disease duration of more than 10 years than those with of less than five years shows that the effect continues throughout the disease period.

In a study examining serum NT-proBNP levels in RA patients at baseline and sixth year of follow-up, the authors found no statistically significant difference, although the levels were increased at the sixth year of follow-up compared to baseline.[16] Similarly, this study also detected an increase in NT-proBNP levels, as the disease duration increased; however, it was not statistically significant.

Fine et al.[17] reported that the LV GLS value of patients with RA was impaired compared to the control group and it was associated with the severity of the disease. In another study, it was shown that LV GLS values of RA patients were impaired and there was a correlation between high NT-proBNP levels and deterioration of GLS values.[18] Although NT-proBNP value was found to be significantly higher in RA patients compared to the control group in the present study, a correlation was not detected between GLS values and NT-proBNP values in layer-specific analysis. The most likely reasons for this may be the characteristics of the patients included in the study and the relatively small number of the study population.

In the study conducted by Magda et al.[19] on how right ventricular (RV) systolic functions were affected in RA patients, subclinical dysfunction developed in the RV in relation to the duration of the disease. In another study, mitral E/A and tricuspid E/A velocities were lower in RA patients.[20] This study also revealed similar results reporting that tricuspid valve A velocity was significantly higher and tricuspid E/A ratio was significantly lower in RA patients compared to the control group. This finding suggests that RV diastolic functions are also impaired in RA patients as the LV functions.

De Rycke et al.[21] showed that the probability of developing extra-articular involvement in anti-CCP-positive RA patients was higher than in negative patients, but they did not find a relationship between RF and extra-articular involvement. In the present study, we found that anti-CCP and RF titers were correlated with strain parameters in all three layers. In the light of these findings, it can be speculated that patients with high titers of anti-CCP and RF may be more prone to subclinical cardiac dysfunction.

There are studies reporting that subclinical myocardial dysfunction occurs in the early stages

of RA and the disease activity is the main determinant of myocardial dysfunction.[22] In the present study, not only the disease activity, but also the disease duration was found to have an impact on subclinical LV dysfunction in RA patients. In contrary to the aforementioned study which did not report a statistically significant difference in mitral E/A velocity in newly diagnosed patients, this study reports that mitral E/A velocity was statistically lower in RA patients with disease duration of >10 years, compared to the control group.

It is well established that high homocysteine is an independent risk factor for coronary heart disease.[23] Vasiljevic et al.[24] reported that homocysteine levels were significantly higher in RA patients and CRP values were positively correlated with high homocysteine levels. A statistically significant increase in plasma homocysteine levels was observed in patients with severe disease activity compared to those with low or moderate disease activity. Yang et al.[25] found higher homocysteine concentrations and did not find any correlation with anti-CCP and RF titers. In this study, no significant difference was detected in homocysteine levels in RA patients and no correlation with immunological parameters (anti-CCP, RF) and DAS28-CRP. In addition, no relationship was found between the disease duration and homocysteine levels. This could be due to the presence of patients whose disease activity was kept under control rather than those with severe disease activity in the sample group and, also the fact that the study type is cross-sectional. Alomari et al.[26] reported that there was no significant difference in homocysteine levels between RA patients and the control group.

Nonetheless, there are some limitations to this study. The insufficient number of the sample group, the fact that the patients did not have very long disease duration, and the heterogeneity of the patient groups may have caused an inability to reveal possible cardiac function changes. However, the results of the data suggest that RA patients have a high risk of cardiovascular disease requiring vigilance for subclinical cardiac dysfunction and should be evaluated with myocardial strain imaging in addition to the standard echocardiography.

In conclusion, the strain values were found to be decreased in all layers with STE examination which allows the detection of subclinical myocardial systolic dysfunction in RA patients. Disease duration and failure to control disease activity were found to be associated with the development of heart failure. The STE can show myocardial deformation at an early stage before the visible changes in the myocardial tissue appear and its use has increased in the recent years. Myocardial dysfunction can be detected in the subclinical period in RA patients with more widespread use of this method. Further large-scale studies evaluating myocardial strain should be conducted on larger number of patients with a wider range of disease duration and activity.

Ethics Committee Approval: The study protocol was approved by the Trakya University Faculty of Medicine Ethics Committee (date: 11.02.2019, no: 52). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: M.E, N.T, M.G, M.E.; Design: M.E, N.T, M.G, M.B; Control/supervision: M.E., N.T, M.G, M.E, M.B, H.E, B,Y, N.S.; Data collection and/or processing, writing the article: M.E, N.T, M.G, M.B, H.E, B.Y.; Analysis and/or interpretation: M.E, N.T, N.S.; literature review: M.E., N.T, M.G, M.E, M.B, H.E, B,Y.; Critical review: M.E., N.T, M.G, M.E, M.B, H.E, B,Y, N.S.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: This study was financially supported by the Trakya University Scientific Research Projects Unit.

REFERENCES

1. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1-26. doi: 10.1002/art.39480.
2. Biskup M, Biskup W, Majdan M, Targońska-Stępniak B. Cardiovascular system changes in rheumatoid arthritis patients with continued low disease activity. Rheumatol Int 2018;38:1207-15. doi: 10.1007/s00296-018-4053-x.

3. Schau T, Gottwald M, Arbach O, Seifert M, Schöpp M, Neuß M, et al. Increased prevalence of diastolic heart failure in patients with rheumatoid arthritis correlates with active disease, but not with treatment type. J Rheumatol 2015;42:2029-37. doi: 10.3899/jrheum.141647.
4. Little WC, Cheng CP. Diastolic dysfunction. Cardiol Rev 1998;6:231-9. doi: 10.1097/00045415-199807000-00011.
5. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81. doi: 10.1002/art.27584.
6. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S14-36. doi: 10.1002/acr.20621.
7. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70. doi: 10.1093/ehjci/jev014.
8. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: Consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16:1-11. doi: 10.1093/ehjci/jeu184.
9. Bansal M, Kasliwal RR. How do I do it? Speckle-tracking echocardiography. Indian Heart J 2013;65:117-23. doi: 10.1016/j.ihj.2012.12.004.
10. Udayakumar N, Venkatesan S, Rajendiran C. Diastolic function abnormalities in rheumatoid arthritis: Relation with duration of disease. Singapore Med J 2007;48:537-42. PMID: 17538753.
11. Midtbø H, Semb AG, Matre K, Kvien TK, Gerdts E. Disease activity is associated with reduced left ventricular systolic myocardial function in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76:371-6. doi: 10.1136/annrheumdis-2016-209223.
12. Sharma A, Kaushik R, Kaushik RM, Kakkar R. Echocardiographic evaluation of diastolic dysfunction in rheumatoid arthritis - a case-control study. Mod Rheumatol 2015;25:552-7. doi: 10.3109/14397595.2014.998404.
13. Naseem M, Samir S, Ibrahim IK, Khedr L, Shahba AAE. 2-D speckle-tracking assessment of left and right ventricular function in rheumatoid arthritis patients with and without disease activity. J Saudi Heart Assoc 2019;31:41-9. doi: 10.1016/j.jsha.2018.10.001.
14. Davis JM 3rd, Lin G, Oh JK, Crowson CS, Achenbach SJ, Therneau TM, et al. Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population. Int J Cardiol 2017;240:379-85. doi: 10.1016/j.ijcard.2017.03.108.
15. Benacka O, Benacka J, Blazicek P, Belansky M, Payer J, Killinger Z, et al. Speckle tracking can detect subclinical myocardial dysfunction in rheumatoid arthritis patients. Bratisl Lek Listy 2017;118:28-33. doi: 10.4149/BLL_2017_006.
16. Targońska-Stępniak B, Piotrowski M, Zwolak R, Drelich-Zbroja A, Majdan M. Prospective assessment of cardiovascular risk parameters in patients with rheumatoid arthritis. Cardiovasc Ultrasound 2018;16:18. doi: 10.1186/s12947-018-0136-9.
17. Fine NM, Crowson CS, Lin G, Oh JK, Villarraga HR, Gabriel SE. Evaluation of myocardial function in patients with rheumatoid arthritis using strain imaging by speckle-tracking echocardiography. Ann Rheum Dis 2014;73:1833-9. doi: 10.1136/annrheumdis-2013-203314.
18. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447-56. doi: 10.1016/j.jacc.2013.09.052.
19. Magda SL, Mincu RI, Florescu M, Ciobanu AO, Udrea GF, Cinteza M, et al. The assessment of subclinical cardiovascular dysfunction in treated rheumatoid arthritis. Maedica (Bucur) 2016;11:267-76.
20. Maloberti A, Riva M, Tadic M, Valena C, Villa P, Boggioni I, et al. Association between atrial, ventricular and vascular morphofunctional alterations in rheumatoid arthritis. High Blood Press Cardiovasc Prev 2018;25:97-104. doi: 10.1007/s40292-017-0246-8.
21. De Rycke L, Peene I, Hoffman IE, Kruithof E, Union A, Meheus L, et al. Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: Diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Ann Rheum Dis 2004;63:1587-93. doi: 10.1136/ard.2003.017574.
22. Lo Gullo A, Rodríguez-Carrio J, Aragona CO, Dattilo G, Zito C, Suárez A, et al. Subclinical impairment of myocardial and endothelial functionality in very early psoriatic and rheumatoid arthritis patients: Association with vitamin D and inflammation. Atherosclerosis 2018;271:214-22. doi: 10.1016/j.atherosclerosis.2018.03.004.
23. Egerton W, Silberberg J, Crooks R, Ray C, Xie L, Dudman N. Serial measures of plasma homocyst(e)ine after acute myocardial infarction. Am J Cardiol 1996;77:759-61. doi: 10.1016/s0002-9149(97)89213-2.
24. Vasiljevic D, Tomic-Lucic A, Zivanovic S, Milosavljevic M, Radovanovic S, Andjelkovic N, et al. Plasma homocysteine concentrations in patients with rheumatoid arthritis. Ser J Exp Clin Res 2015;16:207-11. doi:10.1515/sjecr-2015-0027.

25. Yang X, Gao F, Liu Y. Association of homocysteine with immunological-inflammatory and metabolic laboratory markers and factors in relation to hyperhomocysteinaemia in rheumatoid arthritis. Clin Exp Rheumatol 2015;33:900-3.

26. Alomari MA, Khabour OF, Alawneh K, Shammaa RA. Possible modulation of vascular function measures in rheumatoid arthritis by homocysteine. Int J Rheumatol 2018;2018:8498651. doi: 10.1155/2018/8498651.