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A.O. Baktir[1] · B. Sarli[1] · M.A. Cebicci[2] · H. Saglam[1] · Y. Dogan[1] · M. Demirbaş[2] · S.T. Sutbeyaz[2] · H. Arinc[1]

[1] Department of Cardiology, Kayseri Education and Research Hospital, Kocasinan/Kayseri

[2] Department of Physical Medicine & Rehabilitation, Kayseri Education and Research Hospital, Kayseri

Preclinical impairment of myocardial function in rheumatoid arthritis patients

Detection of myocardial strain by speckle tracking echocardiography

Rheumatoid arthritis is (RA) a chronic, multisystem inflammatory disease which affects about 1% of the general population. Premature mortality among patients with RA occurs frequently due to cardiovascular disease (CVD) including primarily coronary artery disease and heart failure [1, 2]. The incidence of heart failure is higher in patients with RA compared with the general population and the condition contributes to high cardiovascular mortality and morbidity rates [3]. Cardiac involvement in RA is not always symptomatic and may not be detected during a conventional echocardiographic examination. Several echocardiographic studies have demonstrated left ventricular systolic and diastolic dysfunction in RA patients [4]. Most of these studies were conducted using conventional techniques such as Doppler echocardiography, color Doppler M-mode, and tissue Doppler imaging (TDI). Although TDI is considered a reliable tool for the assessment of myocardial deformation, the angle-dependent nature of the method constitutes a limitation. While the myocardium deforms simultaneously in three dimensions, the TDI can only measure the deformation along the ultrasound beam from the myocardial tissue velocities.

Two-dimensional (2D) speckle tracking echocardiography (STE) is a promising new imaging modality that is angle-independent and tracks the myocardial strain along the direction of the myocardial wall in 2D images.

The aim of our study was to investigate the effect of disease duration on myocardial strain in patients with RA.

Patients and methods

The study was conducted on 37 patients [n=16 in the early-stage disease (ESD) group, mean age: 45.7±9 years, female gender n=16; n=21 in advanced-stage disease (ASD) group, mean age: 45.7±16.8 years, female gender n=19] who presented to the Rheumatology Unit of the Kayseri Education and Research Hospital (Kayseri, Turkey) between June 2011 and September 2012 and were diagnosed with RA based on the revised American College of Rheumatology classification criteria [5]. ESD was defined as symptom duration of 5 years or more and ASD was defined as symptom duration of less than 5 years [6]. Approval was obtained from the local ethics committee and informed consent forms were signed by all the patients enrolled. None of the patients had any evidence of cardiac disease, family history of cardiac event, smoking, hypertension, or diabetes mellitus as assessed by the patient history, physical examination, and standard 12-lead electrocardiography (ECG). Other exclusion criteria included technically poor acoustic window, any evidence of cardiac disorders including valvular or congenital heart disease, hypercholesterolemia, arterial hypertension, clinical history and signs or symptoms of coronary artery disease (CAD) or cerebrovascular events, treatment with vasoactive drugs, cardiac rhythm abnormalities, ST-segment or T-wave changes specific for ischemia on the ECG and obesity (body mass index >30 kg/m^2). All patients were examined in terms of the number of tender or swollen joints and underwent laboratory tests for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, and complete blood count.

The echocardiography was performed in the left lateral decubitus position using the GE-Vingmed Vivid 7 (GE-Vingmed Ultrasound AS, Horten, Norway) ultrasound device and a 3S-RS (3.5 MHz) probe. The examinations were performed by two experienced cardiologist who were blinded to the clinical data of the study groups. Images were obtained from the parasternal and apical positions using the 2D, M-mode, and Doppler echocardiographic techniques performed according to the guidelines of the American Society of Echocardiography for the evaluation of left ventricle structures, systolic and diastolic functions, and the calcula-

Tab. 1 Demographic, clinical, and biochemical variables of the patients with early-stage disease (ESD) and advanced-stage disease (ASD)

	ESD		ASD		p
	Mean	SD	Mean	SD	
Age (years)	45.7	±9	45.7	±16.8	0.995
Disease duration (years)	2.8	±1.2	14.6	±6.8	<0.001
Systolic BP (mm/Hg)	123.7	±10	124.3	±9.3	0.961
Diastolic BP (mm/Hg)	79.2	±9.1	77.0	±9.7	0.943
Calcium (mg/dl)	9.6	±0.3	9.5	±0.3	0.285
ALP (U/l)	97.3	±25.5	79.7	±26.3	0.048
ESR (mm/h)	31.0	±20.2	28.9	±21.0	0.762
CRP (mg/dl)	7.1	±5.7	16.1	±13.7	0.018
RF (IU/ml)	89.8	±166.8	111.6	±159.9	0.697
DAS 28	3.9	±0.8	3.5	±0.9	0.163
DMARDs (%)	87.5		85.7		
Corticosteroids (%)	60		52,3		

Data are expressed as mean ± SD. ***CRP*** C-reactive protein, ***DAS-28 score*** low disease activity ≤3.2, moderate disease activity 3.3–5.3, and severe disease activity ≥5.4, ***ESR*** erythrocyte sedimentation rate, ***RF*** rheumatoid factor, ***ALP*** alkaline phosphatase, ***DMARDs*** disease-modifying antirheumatic drugs

Tab. 2 Two-dimensional, M-mode, Doppler, and tissue Doppler echocardiography parameters of patients with early-stage disease (ESD) and advanced-stage disease (ASD)

Parameters	ESD		ASD		p
	Mean	SD	Mean	SD	
LVDD (mm)	44.75	±4.12	45.95	±5.54	0.472
LVSD (mm)	28.50	±2.63	28.62	±3.65	0.913
IVSDD (mm)	9.63	±1.20	9.19	±1.08	0.256
PWDD (mm)	7.19	±3.82	5.81	±3.94	0.293
EF (%)	65.75	±2.98	67.00	±3.26	0.238
LA (mm)	33.19	±3.17	32.05	±3.22	0.29
Mit E (m/s)	0.73	±0.14	0.77	±0.25	0.503
Mit A (m/s)	0.78	±0.13	0.74	±0.27	0.63
Mit E/A (ratio)	0.90	±0.35	1.11	±0.38	0.651
E/E' (ratio)	6.12	±1.96	7.72	±2.70	0.053
Mean S (m/s)	7.97	±1.52	8.14	±2.16	0.786
Mean E (m/s)	11.44	±2.94	10.52	±2.58	0.322
IVRT (m/s)	84.25	±21.70	81.95	±17.89	0.726
DT (m/s)	204.50	±48.50	212.19	±52.51	0.651

Data are expressed as mean ± SD. ***LVDD*** left ventricular diastolic diameter, ***LVSD*** left ventricular systolic diameter, ***IVSDD*** interventricular septum diastolic thickness diameter, ***PWDD*** posterior wall diastolic thickness diameter, ***EF*** ejection fraction, ***LA*** left atrium, ***E*** early diastolic mitral inflow velocities, ***A*** late diastolic mitral inflow velocities, ***E/A*** ratio between diastolic early and late diastolic mitral inflow velocities, ***E/E'*** ratio between early diastolic mitral inflow velocity and early diastolic annular velocity, ***Mean S*** systolic velocity on tissue Doppler echocardiography, ***Mean E*** early diastolic velocity on tissue Doppler echocardiography, ***IVRT*** isovolumic relaxation time, ***DT*** deceleration time

tion of values dependent on the related functions [7].

TDI scans were recorded from the apical four-chamber view using a pulsed-wave Doppler with a 3-mm sample volume placed on the septal and lateral mitral annulus. All of the annular velocities and time intervals of tissue Doppler analyses were calculated as the average of the two annular sites. Pulsed-wave TDI examinations were performed according to the guidelines of the American Society of Echocardiography [8]. The ratios between the mitral early diastolic flow velocity (E) and the mitral annular early diastolic myocardial velocity (E') were calculated. The averages of three consecutive cycles were calculated for all the echocardiographic data.

Offline analyses of the STE from the apical and parasternal short-axis views were carried out using a software package (Echopac PC, version 8.0, GE Healthcare). Standard grayscale 2D images were obtained from the apical four-, two-, and three-chamber views and the parasternal short-axis views at the papillary muscle level at a frame rate of 70–90 frame(s). Myocardial S and strain rate (SR) were measured as previously described [9]. Three consecutive cardiac cycles were recorded at end-expiratory breath holding and stored for the offline analysis. The endocardial border of the left ventricle was manually traced at the end of the end-systolic frame. The software automatically created a region of interest on the entire wall and selected the natural acoustic markers. By tracking these markers frame by frame during the cardiac cycle, the S and SR were measured at any point of the myocardium. The longitudinal strain (L_S), longitudinal systolic strain rate ($L_{SR\text{-}S}$), early diastolic strain rate ($L_{SR\text{-}E}$), and the late diastolic strain rate ($L_{SR\text{-}A}$) were measured from the six left ventricular walls through the recordings made from the apical four-, two-, and three-chamber views. The average values of these measurements were used for the comparison of the patients with ESD and ASD. The radial strain (R_S), radial systolic strain rate ($R_{SR\text{-}S}$), radial early diastolic strain rate ($R_{SR\text{-}E}$), and the radial late diastolic strain rate ($R_{SR\text{-}A}$) were obtained from the parasternal left ventricular short-axis view at the level of the papillary muscles. The circumferential strain (C_S), circumferential systolic strain rate ($C_{SR\text{-}S}$), circumferential early diastolic strain rate ($C_{SR\text{-}E}$), and the circumferential late diastolic strain rate ($C_{SR\text{-}A}$) were also obtained from the same views and the averages were calculated.

Statistical analyses

All analyses were carried out using SPSS16.0 for Windows software package (SPSS Inc., Chicago, Ill., USA). Continuous variables are given as mean ± standard deviation, while categorical variables are defined as percentages. The variables were investigated using the Kolmogorov–Smirnov test to check for the nor-

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Preclinical impairment of myocardial function in rheumatoid arthritis patients. Detection of myocardial strain by speckle tracking echocardiography

Abstract

Objectives. The incidence of heart failure is higher in patients with rheumatoid arthritis (RA) than in the general population and contributes to elevated cardiovascular mortality and morbidity rates. Impaired myocardial function can be detected by a novel echocardiographic method, speckle tracking echocardiography (STE), when conventional methods have yielded normal findings. The aim of our study was to investigate the effect of disease duration on myocardial strain and strain rate parameters in patients with RA.

Methods. This cross-sectional study included 37 RA patients [n=16, female gender n=16, mean age, 45.7±9 years in the early-stage disease (ESD); n= 21, female gender n=19, 45.7±16.8 years in the advanced-stage disease (ASD) group] who were compared according to early disease duration and advanced-stage disease (2.8±1.2 vs. 14.6±6.8 years, respectively). Hypertension, diabetes mellitus, and other cardiovascular risk factors were excluded. Offline analysis of STE was performed and data between the two groups were compared.

Results. R_S, $R_{SR\text{-}E}$, and $R_{SR\text{-}E/A}$ values were statistically significantly lower in patients with ASD. Circumferential strain and strain rate were similar between the two groups. Except for $L_{SR\text{-}E/A}$ values, L_S, $L_{SR\text{-}S}$, $L_{SR\text{-}E}$, and $L_{SR\text{-}A}$ values were decreased in patients with ASD.

Conclusion. RA patients without clinical evidence of cardiovascular disease and in the absence of traditional cardiovascular risk factors can be followed up with STE. In this way, early impairment of myocardial deformation can be detected before the appearance of any clinical evidence of cardiac involvement.

Keywords

Speckle tracking echocardiography · Rheumatoid arthritis · Myocardial strain · Subclinical left ventricular involvement · Disease duration

Subklinische Störung der Myokardfunktion bei Patienten mit rheumatoider Arthritis. Erkennung der Myokarddeformation durch Speckle-Tracking-Echokardiographie

Zusammenfassung

Ziele. Die Inzidenz der Herzinsuffizienz ist bei Patienten mit rheumatoider Arthritis (RA) höher als bei Personen der Allgemeinbevölkerung und trägt zu einer erhöhten kardiovaskulären Mortalitäts- und Morbiditätsrate bei. Eine gestörte Myokardfunktion kann mit einem neuen Echokardiographieverfahren, der Speckle-Tracking-Echokardiographie (STE), erkannt werden, wenn herkömmliche Verfahren einen Normalbefund ergeben haben. Ziel der vorliegenden Studie war es, die Auswirkungen der Krankheitsdauer auf Parameter der Myokarddeformation und Deformationsrate („strain rate") bei Patienten mit RA zu untersuchen.

Methoden. Es wurden 37 RA-Patienten (n=16, weiblich: n=16, Durchschnittsalter: 45,7±9 Jahre in der Gruppe mit frühem Krankheitsstadium bzw. n=21, weiblich: n=19; 45,7±16,8 Jahre in der Gruppe mit fortgeschrittenem Krankheitsstadium) in diese Querschnittsstudie eingeschlossen und in Bezug auf frühes bzw. fortgeschrittenes Krankheitsstadium verglichen (2,8±1,2 Jahre vs. 14,6±6,8 Jahre). Hypertonie, Diabetes mellitus und andere kardiovaskuläre Risikofaktoren wurden ausgeschlossen. Die Auswertung der STE erfolgte offline, und die Daten wurden zwischen den beiden Gruppen verglichen.

Ergebnisse. Die Werte für R_S, $R_{SR\text{-}E}$ und $R_{SR\text{-}E/A}$ waren bei Patienten im fortgeschrittenen Krankheitsstadium statistisch signifikant niedriger als bei denen im frühen Stadium. Zirkumferenzielle Deformation und Deformationsrate waren in beiden Gruppen ähnlich. Mit Ausnahme der Werte für $L_{SR\text{-}E/A}$ waren die Werte für L_S, $L_{SR\text{-}S}$, $L_{SR\text{-}E}$, $L_{SR\text{-}A}$ bei Patienten im fortgeschrittenen Krankheitsstadium vermindert.

Schlussfolgerung. Bei RA-Patienten ohne klinischen Hinweis auf kardiovaskuläre Erkrankungen und ohne herkömmliche kardiovaskuläre Risikofaktoren könnte der Verlauf mittels STE kontrolliert und eine beginnende Störung der Myokarddeformation erkannt werden, bevor es zu klinischen Zeichen einer Herzbeteiligung kommt.

Schlüsselwörter

Speckle-Tracking-Echokardiographie · Rheumatoide Arthritis · Myokarddeformation · Subklinische Störung der linksventrikulären Funktion · Krankheitsdauer

mality of the distribution. The independent samples t test was used to compare the continuous variables between the two groups. Nonparametric values were compared through the Mann–Whitney U test. The chi-square test was used to compare the categorical data. Pearson's correlation was used to correlate continuous variables such as disease duration and parameters of systolic and diastolic function. A two-tailed p value of less than 0.05 was considered as significant.

Results

A total of 37 subjects comprising 16 patients with ESD (female, n=16) and 21 patients with ASD (female, n=19) were evaluated in the study. The demographic, clinical, and biochemical characteristics of both groups are presented in **Tab. 1**. All patients were on treatment with disease-modifying antirheumatic drugs (DMARDs) or corticosteroids or both. None of the patients had signs or symptoms of heart failure. Detailed parameters of the 2D, pulsed Doppler, and TDI examinations of both groups are given in **Tab. 2**. The E/E' ratio was higher in patients with ASD (6.12±1.96 vs. 7.72±2.70; p=0.053) but the difference was statistically insignificant. The differences in the other parameters including the left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVSD), left ventricular ejection fraction (EF), the ratio between the early diastolic and late diastolic mitral inflow velocities (E/A), the interventricular septum diastolic thickness diameter (IVSDD), posterior wall diastolic thickness diameter (PWDD), isovolumic relaxation time (IVRT), systolic velocity on tissue Doppler echocardiography (Mean S), early diastolic velocity on tissue Doppler echocardiography (Mean E), and the deceleration time (DT) were found to be statistically insignificant between the two groups.

Systolic strain, diastolic strain, and strain rate parameters

Detailed 2D-STE values of the groups are presented in **Tab. 3**. The R_S value was lower in the group of patients with ASD than in the patients with ESD and

Tab. 3 Global strain and strain rate parameters of patients with early-stage disease (ESD) and advanced-stage disease (ASD)

	ESD		ASD		p
Radial					
S (%)	58.75	±12.09	43.64	±16.03	0.002
SRS (1/s)	2.51	±0.68	2.51	±0.82	0.995
SRE (1/s)	2.22	±0.53	1.66	±0.54	0.003
SRA (1/s)	1.41	±0.54	1.91	±0.84	0.045
SR E/A	1.88	±0.95	1.07	±0.64	0.004
Circumferential					
S (%)	19.38	±5.76	20.97	±5.10	0.38
SRS (1/s)	1.30	±0.53	1.36	±0.48	0.708
SRE (1/s)	1.59	±0.84	1.44	±0.65	0.545
SRA (1/s)	0.93	±0.67	0.92	±0.57	0.948
SRE/A	2.17	±1.16	2.01	±1.05	0.673
Longitudinal					
S (%)	26.37	±4.30	18.88	±4.67	<0.001
SRS (1/s)	1.87	±0.25	1.14	±0.23	<0.001
SRE (1/s)	2.32	±0.50	1.25	±0.35	<0.001
SRA (1/s)	1.62	±0.37	0.89	±0.29	<0.001
SRE/A	1.51	±0.49	1.51	±0.52	0.999

Data are expressed as mean ± SD and n (%). *A* late diastolic, *E* early diastolic, *S* systolic, *S (%)* strain, *SR* strain rate

the differences were statistically significant. While the $R_{SR\text{-}S}$ values were similar, the $R_{SR\text{-}E}$ and $R_{SR\text{-}E/A}$ values were statistically significantly lower in patients with ASD. There were no differences in terms of the C_S, $C_{SR\text{-}S}$, $C_{SR\text{-}E}$, and $C_{SR\text{-}A}$ values between the groups. The most impressive results were obtained from the longitudinal strain and strain rate parameters. Except for the $L_{SR\text{-}E/A}$ values, the L_S, $L_{SR\text{-}S}$, $L_{SR\text{-}E}$, and the $L_{SR\text{-}A}$ values were observed to have decreased in patients with ASD and the differences were statistically significant. Correlation analysis between the disease duration and strain parameters showed a relationship between $R_{SR\text{-}E}$, $R_{SR\text{-}E/A}$, L_S, $L_{SR\text{-}S}$, $L_{SR\text{-}E}$, and $L_{SR\text{-}A}$ (**Fig. 1a–f**).

Discussion

Our results demonstrate that in patients with RA, the disease duration is significantly associated with the left ventricular deformation parameters measured through 2D-STE imaging.

Cardiac disease is often clinically asymptomatic and is rarely a severely life-threatening complication in RA. An increased risk of CVD including atherosclerosis and heart failure has been demonstrated in epidemiological studies [10]. Necropsy studies of the hearts of patients affected by RA have revealed a high incidence of pericardial, myocardial, and endocardial involvement [11]. In RA patients, heart failure is the result of either systolic or diastolic dysfunction, or both. Patients with RA have been shown to have an approximately twofold risk of heart failure and mortality, which are not explained by the conventional cardiovascular risk factors [12].

Previous studies have already pointed out abnormal conventional Doppler and TDI parameters in RA patients. But most of these studies compared RA patients with healthy subjects. Di Franco et al. [13] demonstrated a strong correlation between the E/A ratio and the duration of disease in patients with RA. Montecucco et al. [14] also reported a correlation between disease duration, 2D left ventricular relaxation parameters, and the E/A ratio in patients with RA. However, Rexhepaj et al. did not observe any correlation between the DT and the duration of RA other than a weak correlation with the E/A ratio. Lastly, Gonzalez-Juanatey et al. [16] and Abdul Muizz et al. [17] did not find any correlation between disease duration and the conventional Doppler parameters of systolic and diastolic left ventricular function [15]. As in previous studies, the mitral flow velocities, DT, and IVRT were not significantly different in our two groups.

TDI is another echocardiographic modality that measures myocardial tissue velocities without the load dependence of other conventional Doppler techniques. TDI studies comparing RA patients and control groups also demonstrated a significant association between the duration of disease and the E/E' ratio [4, 19]. However, similar to the conventional Doppler studies, the reports are conflicting: Although Abdul Muizz et al. [17] found lower E/E' ratios compared with Arslan et al. [4] and Birdane et al. [18], the difference was statistically insignificant between the patients and controls. The present study also demonstrated higher E/E' ratios in the ASD group; however, the difference was statistically insignificant.

Although the TDI is a reliable tool compared with conventional Doppler techniques, the method has limitations such as its angle-dependency and the acquisition of deformation velocities only along the ultrasound beam. Since the study groups from previous studies did not shed any light on the effect of disease duration on the echocardiographic parameters, the present study aimed to compare two groups of RA patients with ESD and ASD. In addition, 2D-STE, which is a new technique involving 2D echographic image analysis, was also employed for the purposes of the study.

STE is a new imaging modality that calculates myocardial velocities and deformation parameters like strain and strain rate. Strain is a dimensionless index of myocardial deformation and is usually expressed in percentage. The strain rate is the difference of strain in a time interval. When left ventricular impairment begins, compensatory mechanisms can still sustain the normal stroke volume. STE can detect reduced contractility even in patients with normal ejection fractions before changes in myocardial tissue velocities and other traditional parameters of systolic function occur [19]. However, the limited evaluation of deformation in the radial plane can be overcome by STE, which represents an emerging algorithm able to analyze echocardiographic images providing objective and reproducible

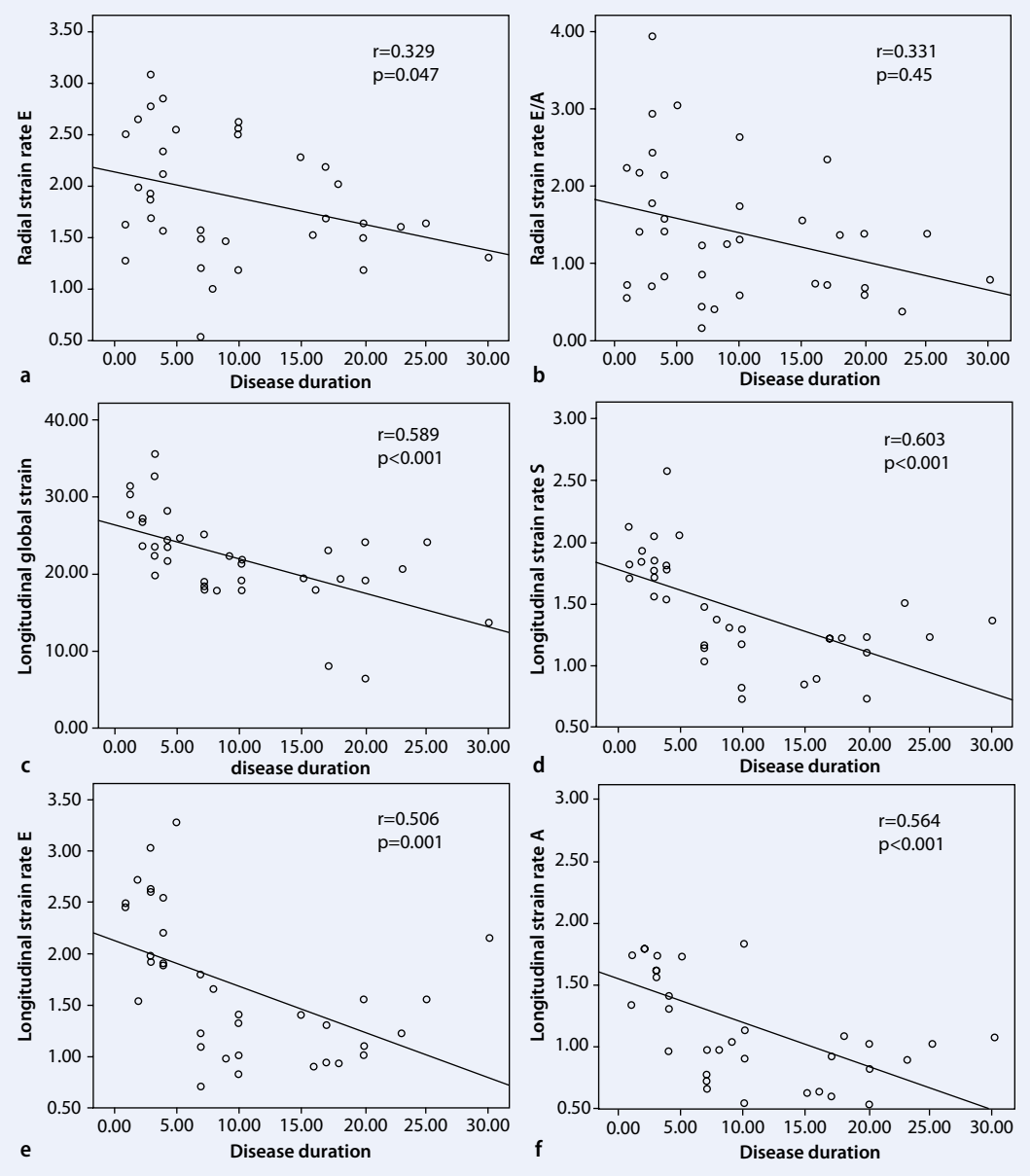

Fig. 1 ◀ **a–f** Correlation analysis between the disease duration and strain parameters show a relationship between $R_{SR\text{-}E}$, $R_{SR\text{-}E/A}$, L_S, $L_{SR\text{-}S}$, $L_{SR\text{-}E}$, and $L_{SR\text{-}A}$

quantification of global myocardial function [20].

Our results demonstrated that in patients with RA, end-systolic radial and longitudinal strain values were reduced in the ASD group. In addition, longitudinal diastolic deformation parameters $L_{SR\text{-}E}$ and $L_{SR\text{-}A}$ and radial diastolic deformation parameters $R_{SR\text{-}E}$, $R_{SR\text{-}A}$, and $R_{SR\text{-}E/A}$ were also significantly reduced in the ASD group. The disease duration and strain parameters demonstrated a statistically significant correlation.

Study limitations

Although there were no differences between the systolic and diastolic blood pressures, we did not take 24-h ambulatory blood pressure recordings. Therefore, we are unable to evaluate possible increases in the blood pressure in RA patients. Since we enrolled RA patients without any cardiovascular risk factors, our investigation included a limited number of patients. We were not able to provide B-type natriuretic peptide (BNP) or nt-pro-BNP values at the time of echocardiography, which could offer more information. Because all our patients were on DMARDs and/or corticosteroids, a comparison of the effects of antirheumatic drugs on disease duration was not feasible. The final limitation of our study was that we could not investigate right ventricular function.

Conclusion

To the best of our knowledge, the present cross-sectional study is a first in terms of evaluating the effects of disease duration based on STE parameters in patients with RA. RA patients without clinical evidence of cardiovascular disease or traditional cardiovascu-

lar risk factors can be followed up using the STE method. In this way, an early impairment in the myocardial deformation can be detected before any clinical evidence of cardiac involvement becomes manifest.

Corresponding address

A.O. Baktir
Department of Cardiology, Kayseri Education and Research Hospital
Sanayi Mah. Atatürk Bulvarı Hastane Cad.
No:78, 38010 Kocasinan/Kayseri
Turkey
aobaktir@gmail.com

Compliance with ethical guidelines

Conflict of interest. A.O. Baktir, B. Sarli, M.A. Cebicci, H. Saglam, Y. Dogan, M. Demirbaş, S.T. Sutbeyaz, and H. Arinc state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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