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ORIGINAL RESEARCH

Three-dimensional Echocardiography for the Early Detection of Cardiac Dysfunction in Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease. Left atrial (LA) dysfunction is strongly linked to cardiovascular diseases, and the early detection of LA function in patients with RA is vital. Real-time three-dimensional echocardiography (RT-3DE) offers a noninvasive method to assess the structure and function of the LA. **Aim of the study:** To assess LA volumes and phasic function in patients with RA using 3D transthoracic echocardiography. **Materials and Methods:** This prospective case-control study included 162 subjects classified into two groups: Group 1 included 82 patients with RA, subdivided into an active RA group (n = 40) and an inactive RA group (n = 42), and Group 2 included 80 healthy matched controls. All study participants were examined using 2D and 3D transthoracic echocardiography. **Results:** Diastolic dysfunction was significantly greater in patients with moderate and severe disease activity than in patients with mild disease activity. RT-3DE analysis of RA groups showed significantly higher maxium, minimum, and pre-atrial LA volumes compared to controls ($p < 0.01$), and these volumes were significantly higher in the active RA group than in the inactive RA group ($p < 0.01$). We also found significantly lower LA passive ejection fraction (EF) and active EF in both RA groups than the control group ($p < 0.01$), and significantly lower total EF in the active RA group than the inactive RA group ($p < 0.01$). **Conclusion:** Patients with RA had increased 3D LA volumes and impaired mechanical function, especially in active RA. RT-3DE provides an accurate measurement of LA volumes and function, being a feasible and reproducible method in clinical applications.

Keywords: left atrium volume, cardiac dysfunction, three-dimensional transthoracic echocardiography, rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease. RA may affect joints, the lungs, skin, eyes, kidneys, nervous system, heart, gastrointestinal tract, and blood vessels, and cause severe pain and incapacity, as well as premature death. Patients with RA account for around 0.5–1% of the world's population.[1] The involvement of the cardiovascular system is diverse in patients with RA, yet it is asymptomatic in many of them, and RA was reported as an independent risk factor for cardiovascular disease.[2] The prevalence of cardiovascular disease is two to five times higher in patients with RA compared to the general population, and patients with RA have a higher risk of abnormal cardiac function and structure, even without a history of heart disease.[3] The leading cause of death in patients with RA is related to cardiac involvement.[4] Therefore, in these patients, the early assessment of myocardial function is important to ensure that other clinical decisions are suitable. This can reduce mortality caused by the high incidence of cardiovascular complications with occult onset in patients with RA. The volume and function of the left atrium (LA) serve as valuable predictors of cardiovascular events such as atrial fibrillation (AF), congestive heart failure, stroke, and death.[5] Therefore, the evaluation of the volume and function of the LA is vital in these clinical settings. However, few studies have assessed LA function in patients with RA.

LA enlargement and dysfunction can predict the occurrence of AF in patients with sinus rhythm, especially in patients with RA. AF is associated with three significant complications that may be considered a cardiovascular emergency: thromboembolism, hemodynamic instability, and arrhythmogenesis. In patients with AF, the incidence of embolization is about 5% per year. The risk of embolism and stroke can be reduced by warfarin anticoagulation. The hemodynamic complications of atrial fibrillation may be caused by the loss of effective atrial contraction, the irregular ventricular rhythm, and the excessively rapid ventricular rate. In patients with Wolff-Parkinson-White syndrome, AF can cause sudden cardiac death. Torsades de pointes is perhaps the most widely recognized arrhythmia caused by drugs used in the treatment of AF, especially type 1A antiarrhythmic drugs and sotalol. Chronic treatment with type 1C drugs may also induce atrial flutter with significant hemodynamic instability in 3.5–5% of patients.[1–7]

Although angiography can precisely assess LA function, current imaging techniques, such as two- and three-dimensional echocardiography (3DE), cardiac resonance imaging, and multidetector computed tomography (CT) allow for a detailed evaluation of the LA. The development of 3DE has significantly improved our knowledge and management of cardiac illnesses in clinical practice.[6] Three-dimensional transthoracic echocardiography facilitates a more precise and reproducible interpretation of complex cardiac anatomy. Its accuracy is superior to that of conventional echocardiography and eliminates the need for geometric assumptions during chamber volume measurements.[7] Based on these considerations, our study aims to provide an overview of the 3DE assessment of LA volumes and phasic functions in patients with RA. Three-dimensional transthoracic echocardiography is used to assess LA volumes and phasic function in patients with RA as a tool for early predicting cardiovascular diseases.

MATERIALS AND METHODS

This prospective case–control study was conducted at the Department of Cardiology and the Department of Rheumatology and Physical Rehabilitation of Minia University Hospital between September 2019 and September 2020. The study included 162 subjects classified into two groups. Group 1 included 82 patients with RA, and Group 2 included 80 healthy matched controls. Patients with RA were classified into two subgroups: the active RA group, which included 40 patients with a disease activity score 28 for RA with C-reactive protein (CRP) (DAS-28-CRP) >2.6, and the inactive RA group, which included 42 patients with a DAS-28-CRP <2.6. Patients with RA fulfilled the 2010 ACR-EULAR classification criteria of RA.[8] Patients with hypertension, diabetes mellitus, smokers, those with pre-existing cardiac diseases (echocardiographic evidence of global or regional wall motion abnormalities, significant valvular heart disease, AF, congenital heart disease), advanced renal disease, advanced liver disease, chronic obstructive airway diseases, or poor image quality were excluded.

The study obtained ethical approval from the Research Ethics Committee of the Faculty of Medicine, Minia University, and all patients provided written consent before inclusion. Based on DAS-28-CRP, disease activity was classified as remission (score ≤2.6), mild (2.6–3.2), moderate (3.2–5.1), and severe (>5.1).[9,10]

Clinical examination and laboratory investigations were performed for all study participants. Laboratory investigations included the erythrocyte sedimentation rate, complete blood count, and serum levels of CRP, rheumatoid factor, and anti-CCP. Conventional 2D transthoracic echocardiography (IE33, Philips Medical System) was performed for all patients in accordance with the 2015 recommendations of the American Society of Echocardiogra-

phy. LA function was assessed by measuring LA volumes using the biplane Simpson's method.

M-mode echocardiography under 2D guidance was used to determine left ventricular (LV) end-diastolic and end-systolic diameters in parasternal long-axis view. LV posterior wall thickness, diastolic interventricular septum, and LA diameter were recorded from the same views. The apical four-chamber view recorded mitral inflow using conventional pulsed Doppler imaging. 3DE was performed by a single experienced cardiologist blinded to clinical data with an X3 matrix-array transducer (13 MHz) to find 'full volume' real-time pyramidal volumetric data sets along four consecutive cardiac cycles. The participants were instructed to hold their breath in the left lateral decubitus position, and images were synchronized with electrocardiographic records. During expiration, the apical two- and four-chamber images were extracted from the set of pyramidal data. The scanning volume encompassed the LA gap. Subsequently, the real-time 3DE (RT-3DE) data sets were numerically archived for analysis with QLab-Philips software.

STATISTICAL ANALYSIS

Statistical analyses were carried out using SPSS software (version 20, IBM, NY, USA). Categorical variables were expressed through number (n) and percentage (%), and numerical variables as mean ± standard deviation (SD). Normal distribution of the data was verified using the Kolmogorov–Smirnov test. Quantitative variables were compared using the t-test, one-way analysis of variance (ANOVA), and Duncan test, whereas categorical variables were compared using the chi-squared test was used. The level of statistical significance was set at $p \leq 0.05$.

ETHICS

The study protocol was approved by the ethics committee of the Faculty of Medicine of Minia University. All participants provided written informed consent before being included in the study, and all study procedures were carried out in accordance with relevant guidelines and regulations.

RESULTS

Table 1 presents a detailed summary of the study population's baseline characteristics. The three groups were comparable regarding age and sex, while the groups of patients with RA had significantly higher body mass index and body surface area than the control group. Disease

TABLE 1. Baseline characteristics, clinical and laboratory data in the study groups

Variable	Active RA group (n = 40)	Inactive RA group (n = 42)	Control group (n = 80)	p value
Age (years)	45.7 ± 6.5	46.8 ± 5.8	44.5 ± 8.3	0.25
Sex (male/female)	17/23	19/23	33/47	0.91
Body mass index (kg/m^2)	22.9 ± 3.8	21.8 ± 3.8	20.1 ± 3.3	<0.01
Body surface area (m^2)	2.09 ± 0.12	2.08 ± 0.12	1.94 ± 0.11	<0.01
Disease duration (years)	16.5 ± 2.5	10.1 ± 2.2	–	<0.01
HCQ (%)	16 (40.0%)	16 (38.1%)	–	1.0
Systolic blood pressure (mmHg)	117.1 ± 3.9	115.7 ± 4.7	114.5 ± 4.8	<0.01
Diastolic blood pressure (mmHg)	74.5 ± 3.2	76.9 ± 3.5	78.1 ± 3.6	<0.01
Heart rate (bpm)	85.3 ± 7.5	82.3 ± 7.4	83.8 ± 8.7	0.25
Respiration rate (breaths/min)	14.4 ± 2.9	15.1 ± 2.1	14.9 ± 2.4	0.41
28 tender joint count	12.3 ± 2.4	3.3 ± 0.9	–	<0.01
28 swollen joint count	10.3 ± 1.8	2.1 ± 1.1	–	<0.01
Dry eye	11.3 ± 2.8	4.3 ± 1.2	–	<0.01
Morning stiffness (min)	46.7 ± 10.5	13.7 ± 1.2	–	<0.01
Random blood glucose (mg/dL)	90.2 ± 6.3	92.8 ± 4.7	80.3 ± 13.7	<0.01
1st h erythrocyte sedimentation rate (mm/h)	53.3 ± 4.6	21.3 ± 11.2	10.3 ± 2.1	<0.01
2nd h erythrocyte sedimentation rate (mm/h)	80.7 ± 18.5	43.4 ± 17.6	19.3 ± 1.9	<0.01
C-reactive protein (mg/L)	22.6 ± 10.6	11.7 ± 5.1	1.20 ± 2.4	<0.01
Rheumatoid factor positive (n, %)	26 (65.0%)	12 (28.6%)	–	<0.01
Anti-CCP (n, %)	16 (40.0%)	2 (4.8%)	–	<0.01

TABLE 2. 2D echocardiography parameters in the study groups

Variable	Active RA group (n = 40)	Inactive RA group (n = 42)	Control group (n = 80)	p value
LVEDD (mm)	41.9 ± 3.6	41.2 ± 4.6	40.9 ± 5.6	0.58
LVESD (mm)	28.1 ± 2.24	29.1 ± 2.65	28.5 ± 2.21	0.15
SWT (mm)	7.70 ± 0.83	7.63 ± 0.85	7.51 ± 0.70	0.41
PWT (mm)	7.33 ± 0.96	7.23 ± 0.90	7.13 ± 0.85	0.50
LVEF	67.0 ± 6.5	65.1 ± 4.7	66.5 ± 5.9	0.29
Peak E velocity (cm/s)	88.7 ± 2.9	87.7 ± 2.4	85.3 ± 3.5	<0.01
Peak A velocity(cm/s)	80.7 ± 5.9	81.1 ± 7.2	84.6 ± 4.5	<0.01
Lateral E prime (E`) (cm/s)	9.77 ± 0.77	9.60 ± 1.83	8.17 ± 0.91	<0.01
Septal E prime (E`) (cm/s)	6.72 ± 0.89	7.66 ± 0.76	5.33 ± 0.80	<0.01
E/A ratio	12.7 ± 1.8	11.3 ± 1.1	16.2 ± 2.6	<0.01
E/E′ ratio	13.0 ± 3.4	8.5 ± 3.5	7.6 ± 0.3	<0.01
Deceleration time (ms)	178.2 ± 32.3	171.2 ± 24.2	169.1 ± 30.5	0.27
LAV_{max} (mL/m^2)	43.4 ± 5.9	39.3 ± 3.1	33.3 ± 1.7	<0.01
LAV_{min} (mL/m^2)	17.7 ± 1.5	15.7 ± 1.0	13.3 ± 0.7	<0.01
LAV_{preA} (ml/m^2)	31.1 ± 1.6	30.2 ± 1.6	24.5 ± 1.0	<0.01
LA minimum diameter (mm)	42.3 ± 1.3	42.6 ± 1.4	38.5 ± 6.6	<0.01
LA maximum diameter (mm)	50.8 ± 1.7	51.1 ± 1.5	46.6 ± 0.7	<0.01

A, mitral late diastolic; E, mitral early diastolic

duration was significantly longer in the active RA group. Systolic blood pressure values and glycemia were significantly higher in the RA groups than in controls; however, heart and respiration rates were comparable. In the first 2 h, erythrocyte sedimentation rate and CRP values were higher in patients with RA than in the control group (p <0.01). We found a statistically significant difference regarding the prevalence of diastolic dysfunction between cases with moderate and severe disease activity (100% in both) and cases with mild activity (72.7%) (p <0.01).

Table 2 presents data on various 2D echocardiography parameters, including left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), septal wall thickness (SWT), posterior wall thickness (PWT), Doppler and tissue Doppler echocardiography parameters,

TABLE 3. RT-3DE volume and function parameters in the study groups

Variable	Active RA group (n = 40)	Inactive RA group (n = 42)	Control group (n = 80)	p value
LAV_{max} (mL)	39.9 ± 2.3	37.2 ± 1.1	37.1 ± 1.2	<0.01
Indexed 3D LAV_{max} (mL/m^2)	48.9 ± 2.0	44.9 ± 0.7	42.6 ± 0.7	<0.01
LAV_{min} (mL)	15.8 ± 1.1	13.8 ± 1.1	12.9 ± 0.9	<0.01
Indexed 3D LAV_{min} (mL/m^2)	22.1 ± 1.0	19.4 ± 1.6	17.1 ± 1.0	<0.01
3D LAV_{preA} (mL)	22.4 ± 1.0	21.9 ± 1.4	18.8 ± 0.8	<0.01
Indexed 3D LAV_{preA} (mL/m^2)	88.7 ± 2.9	87.7 ± 2.4	85.3 ± 3.5	<0.01
3D LA TEV (mL)	23.1 ± 2.9	23.5 ± 1.4	23.8 ± 1.6	0.18
3D LA TEF (%)	58.8 ± 6.7	62.9 ± 3.2	63.8 ± 2.7	<0.01
3D LA AEV (mL)	6.71 ± 1.41	7.03 ± 1.99	6.41 ± 1.98	0.21
3D LA AEF (%)	29.4 ± 5.5	35.9 ± 6.9	31.4 ± 4.6	<0.01
3D LA PEV (mL)	11.2 ± 3.9	10.7 ± 2.4	11.5 ± 3.4	0.45
3D LA PEF (%)	42.7 ± 4.4	40.6 ± 4.1	48.1 ± 4.9	<0.01
EI	147.4 ± 21.3	172 ± 20.9	188.4 ± 20.8	<0.01

TEV, total emptying volume; AEV, active emptying volume; PEV, passive emptying volume

TABLE 4. Comparison between 2D and 3D in indexed LAV_{max}, indexed LAV_{min}, and indexed LAV_{preA} between groups

Variable	Active RA group (n = 40)	Inactive RA group (n = 42)	Control group (n = 80)	p value
Indexed 2D LAV_{max} (mL)	43.4 ± 5.9	39.3 ± 3.1	33.3 ± 1.7	<0.01
Indexed 3D LAV_{max} (mL/m²)	48.9 ± 2.0	44.9 ± 0.7	42.6 ± 0.7	<0.01
p value	<0.01	<0.01	<0.01	
Indexed 2D LAV_{min} (mL)	17.7 ± 1.5	15.7 ± 1.0	13.3 ± 0.7	<0.01
Indexed 3D LAV_{min} (mL/m²)	22.1 ± 1.0	19.4 ± 1.6	17.1 ± 1.0	<0.01
p value	<0.01	<0.01	<0.01	
Indexed 2D LAV_{preA} (mL)	31.1 ± 1.6	30.2 ± 1.6	24.5 ± 1.0	<0.01
Indexed 3D LAV_{preA} (mL/m²)	38.1± 1.5	34.9± 1.4	32.1± 1.0	<0.01
p value	<0.01	<0.01	<0.01	

ANOVA test and t-test were used to compare the groups.

indexed 2D maximum and minimum LA volume (LAV) (LAV_{max} and LAV_{min}), indexed 2D LA pre-atrial contraction volume (LAV_{preA}), 2D LA diameters, and E/A and E/E' ratios. We found no significant differences between patient groups with regard to LVESD, LVEDD, SWT, PWT, LVEF, and LA diameters. The E/A ratio was lower, and the E/E′ ratio and deceleration time were higher in patients with RA than in the control group. Left ventricular diastolic dysfunction (LVDD) was considerably more common in patients with RA, being present in 60 patients with RA (73%, of which 45 patients had grade 1 and 15 patients had grade 2 LVDD) and in 12 controls (15.0%, all with grade 1 LVDD) (p <0.01). A velocity, E velocity, E/A ratio, E′ velocity, and A′ velocity were nearly identical in both RA groups, while E/E` and deceleration time were significantly higher in the active RA group (p <0.01).

VEDD, LVESD, SWT, PWT, and LVEF showed no significant differences among the groups (p >0.05), indicating that the active RA and inactive RA groups were comparable to the control group in terms of LV dimensions and ejection fraction. Peak E velocity, peak A velocity, E`, E/A ratio, E/E` ratio, LAV, and 2D LA showed significant differences between groups (p <0.01).

As far as RT-3DE parameters are concerned, LAV_{max}, LAV_{min}, and LAV_{preA} were significantly higher in patients with RA than in controls (Table 3), and the passive emptying fraction (PEF), the total emptying fraction (TEF), the active emptying fraction (AEF), and the expansion index (EI) were significantly lower in patients with RA than in controls. We found no significant differences between groups regarding total emptying (stroke) volume and active and passive emptying volume. The active RA group exhibited significantly increased LAV_{max}, LAV_{min}, and LAV_{preA} compared to the inactive RA group (p <0.01). TEF, AEF, PEF, and EI were lower in the active RA group than in the inactive RA group (p <0.01). Disease activity is associated with increased LA volumes, highlighted by the 3DE measurements presented in Table 4. LAV_{max}, LAV_{min}, and LAV_{preA} measured with 3DE were the largest in the active RA group, followed by the inactive RA group, and the control group (p <0.01).

DISCUSSION

RA is a chronic systemic inflammatory disease that affects mainly synovial joints. Patients with RA may have a higher chance of cardiovascular morbidity and mortality than the general population.[1] The LA is essential in regulating LV filling and optimizing overall cardiac function, and many imaging methods have been used to evaluate LA dynamics. This study aimed to assess LA volumes and phasic function in patients with RA using 3D transthoracic echocardiography. An enlarged LA may signal increased severity in congestive heart failure or myocardial infarction. Furthermore, the enlargement of the LA serves as a robust echocardiographic predictor for the risk of non-rheumatic AF. This condition, in turn, is a primary risk factor for stroke, which is linked to a two-fold increase in all-cause mortality. RT-3DE and speckle-tracking echocardiography have introduced a novel imaging approach, enabling a more precise, sensitive, and repeatable assessment of LA size and function.

In this study, RT-3DE analysis found significantly higher LAV_{max}, LAV_{min}, and LAV_{preA} values in the active RA and inactive RA groups compared to controls (p <0.01), and these values were significantly higher in active RA than in inactive RA (p <0.01). All LA volumes measured using RT-3DE were significantly larger compared to the corresponding 2D measurements (p <0.01), demonstrating the higher sensitivity of RT-3DE compared to 2D

echocardiography. Furthermore, we found lower PEF and AEF in both RA groups than the control group ($p < 0.01$) and significantly lower TEF in the active RA group than the inactive RA group ($p < 0.01$). Both RA groups showed significantly lower EI and TEF than the control group ($p < 0.01$), and the active RA group showed a lower EI and TEF than the inactive RA group ($p < 0.01$). We also found that RA activity was connected with the stage of LA enlargement and mechanical dysfunction.

To the best of our knowledge, this is the first study to assess LA volume and function using RT-3DE in patients with RA. Our results are in agreement with those of a similar recent study by Rohner *et al.*,[11] who determined LAV_{max}, LAV_{min} and TEF and compared the results using CT. They found significant correlations between RT-3DE and CT measurements for LAV_{max} ($p = 0.001$), LAV_{min} ($p < 0.001$), and TEF ($p < 0.001$). LAV_{min} and LAV_{max} were lower with RT-3DE than with CT ($p < 0.001$), whereas TEF was higher with RT-3DE ($p < 0.001$). In a study by Iwataki *et al.*,[12] 2D and 3D transthoracic echocardiography was used to measure the LAV indexed to BSA in 200 subjects by employing the biplane Simpson's method. Mean LAV measured with the 3D volumetric method was substantially lower than with multidetector CT. The authors found a significant correlation between the two methods ($r = 0.97$, $p < 0.001$) with acceptable limits of agreement, and a strong correlation between the 3D biplane Simpson's method and 3D volumetric methods ($r = 0.99$, $p < 0.001$). Iwataki *et al.*[12] concluded that LAV could be determined accurately using the 3D biplane Simpson's method.

Most patients with RA have increased oxidative stress, elevated levels of pro-inflammatory cytokines, and activation of immune cells due to the persistent inflammatory condition associated with RA. These factors contribute to the development of myocarditis, microvascular diseases, or epicardial coronary arthritis.[1] The remodeling of the LA, which occurs due to pressure and/or volume overload, indicates the severity and chronic nature of underlying pathological conditions rather than an immediate reflection of LV diastolic dysfunction and filling pressure. As such, the extent and degree of LA dilation are associated with the severity of the disease, highlighting its progression.[13] Galarza-Delgado *et al.*[14] reported that LA dilation was found in 14.3% of patients with RA compared to no cases in the control group ($p = 0.01$). LA dilation was defined as a LA indexed volume (LAIV) of >34 mL/m^2. Also, it has been reported that LV diastolic dysfunction is common in RA and results in increased left intraventricular pressure during diastole, resulting in LA dilatation and declining LA conduction. RA may also directly impact the LA, inducing dilation and stiffness.[15]

In this study, 75% of patients with RA have been diagnosed with a type 1 diastolic dysfunction, higher than what was reported by Liang *et al.*[16] in a cross-sectional study that compared adults with and without RA who did not exhibit clinical signs of heart failure, using 2D echocardiography. A total of 244 subjects with RA with an average age of 60.5 years were included in the study. The findings revealed a 31% prevalence of diastolic dysfunction in this group, demonstrating a positive correlation with the duration of the disease.[16] Similarly, several studies have confirmed the presence of diastolic dysfunction and lowering of the E/A ratio in patients with RA compared to the control group. Arslan *et al.*[17] conducted a study involving 52 individuals diagnosed with RA and 47 without RA to evaluate left ventricular diastolic function, analyzing tissue Doppler imaging and transmitral flow. The findings revealed a significantly lower E/A ratio in patients with RA compared to the control group. In a study by Udayakumar *et al.*[18] on 45 patients with RA, LVDD had a very high prevalence among patients with RA; however, no evident cardiovascular disease was observed compared to the control group.

Our results revealed that there is a significant positive correlation between LVDD and disease activity, as indicated by the DAS-28-CRP score. This finding is agreement with those reported by Carlos *et al.*[19] Targońska-Stępniak *et al.*[20] reported that diastolic dysfunction and RA activity are significantly correlated, which is attributed to the association of active disease with interstitial fibrosis and decreased LV compliance, leading to diastolic dysfunction and atrial myopathy.

RA also affects the conduction function of the LA. Nikitin *et al.*[21] found that LA conduction is mainly determined by the rate of LV relaxation, which may explain the reduced PEF in RA with impaired LVDD. Changes in LA conduction caused by impaired LV relaxation are reflected by changes in mitral inflow E/A ratio. Anwar *et al.*[22] reported that conduction impairment leads to an increased LAVpreA, inducing an increase of LA active function due to the elongation of cardiac muscle fibers, which helps compensate for the enhanced hemodynamic load. Further expansion of LAV reduces contractility. The compensatory increase in the pump function of the LA is expected in LVDD, as the impaired compliance of the LV hinders diastolic filling. However, a decrease in LA pump and reservoir function was observed in patients with RA, suggesting impairment of the intrinsic determinants of LA mechanical function and LV diastolic function in these patients.

Our results also suggest that disease activity is associated with cardiovascular dysfunction. These findings are in accordance with those reported by Huaranga *et al.*[23] in a cross-sectional, observational, analytical study. In their cohort, disease activity level across the simple disease activity index (SDAI) was found to be a risk factor for the development of atheromatous plaques (OR 4.95; p = 0.008). A cross-sectional study by Hanvivadhanakul and Buakhamsri,[24] which analyzed 60 patients with RA using conventional and strain echocardiography, found no significant differences between groups regarding LV volumes, LVEF, normal limits of LV diastolic function, and global longitudinal strain in patients compared to the control group. Similarly, Gürkan *et al.*[25] and Rudominer *et al.*[26] found no significant differences in the prevalence of diastolic dysfunction in patients with RA and the control group. In an echocardiographic and Doppler study, Abo Malek *et al.*[27] reported similar results (47.2% in patients with RA vs. 50.9% in the control group) and found no significant association between diastolic function and DAS-28 values in patients with RA.

This study has some limitations. The lack of patient follow-up diminishes the power of our findings. In order to establish the predictive value of LA mechanical volume and function assessment in patients with RA, it is essential to conduct large-scale prospective studies with long-term follow-up. Another challenge is represented by the reduced resolution of 3D imaging compared to 2D imaging. Furthermore, we opted not to incorporate the LA appendage in calculating LAV owing to the inherent challenges in measuring its variable shape and the absence of universally established reference values for its normal volume. Therefore, we considered excluding the LA appendage a reasonable approach.

CONCLUSIONS

Echocardiographic examination may aid the identification of subjects at increased risk for stroke and death. It may provide insights into the pathogenesis of stroke, being essential in the therapeutic management of this condition. On 3DE, patients with RA had increased LA volumes with impaired mechanical function, especially in cases with increased disease activity. RT-3DE enables the precise measurement of LA volumes and function, being a feasible and reproducible method in clinical applications. One of its notable advantages is the 3D visualization of the LA, eliminating the reliance on geometric assumptions. These favorable characteristics make RT-3DE an effective tool for assessing LA volumes and function in clinical practice. Large-scale, long-term prospective studies are needed to assess the predictive value of LA volumes in patients with RA.

DATA AVAILABILITY

The datasets generated and/or analyzed in this study are not publicly available due to patient confidentiality and informed consent, but may be obtained from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Smolen JS, Aletaha D, Mclinnes IB. Rheumatoid arthritis. Lancet. 2016;388:2023–2038. doi: 10.1016/S0140-6736(16)30173-8.
2. Vizzardi E, Cavazzana I, Bazzani C, Pezzali N, Ceribelli A, Bonadei et al. Echocardiographic evaluation of asymptomatic patients affected by rheumatoid arthritis. J Investig Med. 2012;60:1204¬¬–1208. doi: 10.2310/JIM.0b013e3182746a83.
3. Atzeni F, Sarzi-Puttini P. Early rheumatoid arthritis. Reumatismo. 2007;59:100–117.
4. Buleu F, Sirbu E, Caraba A, Dragan S. Heart involvement in inflammatory rheumatic diseases: A systematic literature review. Medicine (Kaunas). 2019;55:249. doi: 10.3390/medicina55060249.
5. Chirinos JA, Sardana M, Ansari B, et al. Left Atrial Phasic Function by Cardiac Magnetic Resonance Feature Tracking Is a Strong Predictor of Incident Cardiovascular Events. Circ Cardiovasc Imaging. 2018;11:e007512. doi: 10.1161/CIRCIMAGING.117.007512.
6. Boyd AC, Thomas LJC. Left atrial volumes: two-dimensional, three-dimensional. Curr Opin Cardiol. 2014;29:408–416. doi: 10.1097/HCO.0000000000000087.
7. England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. BMJ. 2018;23:361:k1036. doi: 10.1136/bmj.k1036.
8. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–2581. doi: 10.1002/art.27584.
9. Boyadzhieva V, Stoilov N, Ivanova M, Petrova G, Stoilov R. Real World Experience of Disease Activity in Patients With Rheumatoid Arthritis and Response to Treatment With Varios Biologic DMARDs. Front Pharmacol. 2018;20:1303. doi: 10.3389/fphar.2018.01303.
10. Bruce, B, Fries JF. The health assessment questionnaire (HAQ). Clin Exp Rheumatol. 2005;23:S14.
11. Rohner A, Brinkert M, Kawel N, et al. Functional assessment of the left atrium by real-time three-dimensional echocardiography using a novel dedicated analysis tool: initial validation studies in comparison with computed tomography. Eur J Echocardiogr. 2011;12:497–505. doi: 10.1093/ejechocard/jer066.

12. Iwataki M, Takeuchi M, Otani K, et al. Measurement of left atrial volume from transthoracic three-dimensional echocardiographic datasets using the biplane Simpson's technique. J Am Soc Echocardiogr. 2012;25:1319–1326. doi: 10.1016/j.echo.2012.08.017.
13. Wu VC, Takeuchi M. Three-Dimensional Echocardiography: Current Status and Real-Life Applications. Acta Cardiol Sin. 2017;33:107–118. doi: 10.6515/acs20160818a.
14. Galarza-Delgado D, Azpiri-López J, Colunga-Pedraza I, et al. AB0360 Left atrial dilation is increased in patients with rheumatoid arthritis: a case-control study. Annals of the Rheumatic Diseases. 2018;77:1351–1352.
15. Hsiao SH, Lin KL, Chiou KR. Comparison of left atrial volume parameters in detecting left ventricular diastolic dysfunction versus tissue Doppler recordings. Am J Cardiol. 2012;109:748–755. doi: 10.1016/j.amjcard.2011.10.040.
16. Liang KP, Myasoedova E, Crowson CS, et al. Increased prevalence of diastolic dysfunction in rheumatoid arthritis. Ann Rheum Dis. 2010;69:1665–1670. doi: 10.1136/ard.2009.124362.
17. Arslan S, Bozkurt E, Sari RA, Erol MK. Diastolic function abnormalities in active rheumatoid arthritis evaluation by conventional Doppler and tissue Doppler: relation with duration of disease. Clin Rheumatol. 2006;25:294–299. doi: 10.1007/s10067-005-0014-3.
18. Udayakumar N, Venkatesan S, Rajendiran C. Diastolic function abnormalities in rheumatoid arthritis: relation with duration of disease. Singapore Med J. 2007;48:537–542.
19. Carlos E, Alexander L, Mithun P, Jose N, Debabrata M. Prevalence and predictors of left ventricular diastolic dysfunction in a Hispanic patient population. Int J Angiol. 2013;22:229–234. doi: 10.1055/s-0033-1353240.
20. Targońska-Stępniak B, Biskup M, Biskup W, Majdan M. Diastolic dysfunction in rheumatoid arthritis patients with low disease activity. Clinical Rheumatology. 2019;38:1131–1137. doi: 10.1007/s10067-018-4369-7.
21. Nikitin NP, Witte KK, Thackray SD, Goodge LJ, Clark AL, Cleland JG. Effect of age and sex on left atrial morphology and function. Eur J Echocardiogr. 2003;4:36–42. doi: 10.1053/euje.2002.0611.
22. Anwar AM, Geleijnse ML, Soliman OI, Nemes A, Ten Cate FJ. Left atrial Frank-Starling law assessed by real-time, three-dimensional echocardiographic left atrial volume changes. Heart. 2007;93:1393–1397. doi: 10.1136/hrt.2006.099366.
23. Ramírez Huaranga MA, Mínguez Sánchez MD, Zarca Díaz de la Espina MÁ, Espinosa Prados PJ, Romero Aguilera G. What role does rheumatoid arthritis disease activity have in cardiovascular risk? Reumatol Clin (Engl Ed). 2018;14:339–345. doi: 10.1016/j.reuma.2017.03.013.
24. Hanvivadhanakul P, Buakhamsri A. Disease activity is associated with LV dysfunction in rheumatoid arthritis patients without clinical cardiovascular disease. Adv Rheumatol. 2019;59:56. doi: 10.1186/s42358-019-0100-x.
25. Acar G, Sayarlioğlu M, Akçay A, et al. Evaluation of atrial electromechanical delay and left atrial mechanical functions in patients with rheumatoid arthritis. Turk Kardiyol Dern Ars. 2009;37:447–453.
26. Rudominer RL, Roman MJ, Devereux RB, et al. Independent association of rheumatoid arthritis with increased left ventricular mass but not with reduced ejection fraction. Arthritis Rheum. 2009;60:22–29. doi: 10.1002/art.24148.
27. Abdul Muizz AM, Mohd Shahrir MS, Sazliyana S, Oteh M, Shamsul AS, Hussein H. A cross-sectional study of diastolic dysfunction in rheumatoid arthritis and its association with disease activity. Int J Rheum Dis. 2011;14:18–30. doi: 10.1111/j.1756-185X.2010.01593.x.