

Diastolic dysfunction in patients with rheumatoid arthritis

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Objective

The aim of this study was to evaluate left ventricular diastolic function parameters as an early predictor of cardiac involvement in patients with rheumatoid arthritis (RA) without any evidence of hypertension, diabetes mellitus, rheumatic fever or underlying cardiac disease, detected by Doppler echocardiography and to correlate diastolic function in RA patients with different RA disease characteristics.

Patients and methods

Seventy-five RA patients were diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA and another 38 age-matched and sex-matched healthy participants were included. All patients and the control groups were submitted to M-mode, two-dimensional, Doppler (continuous and pulsed wave) echocardiography. Diastolic dysfunction was defined as when transmitral flow E/A ratio is less than one.

Results

Left ventricular diastolic dysfunction was found in 28 (37.3%) of 75 RA patients and four (10.5%) of 38 controls with a *P* value of less than 0.05. In the patients' group, a statistically significant correlation was found between diastolic dysfunction and duration of the disease ($P < 0.05$), and disease activity was assessed by 28 Joint Disease Activity Score ($P < 0.05$).

Conclusion

Among those without a history of cardiac disease, patients with RA have a higher prevalence of diastolic dysfunction than those without RA. Diastolic dysfunction in RA was associated with disease duration and disease activity. Thus, early identification of diastolic dysfunction in asymptomatic RA patients by the use of echocardiography may provide an opportunity to manage the underlying etiology to prevent progression to diastolic heart failure.

Keywords:

diastolic dysfunction, echocardiography, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation and deterioration of the joints, which can produce a loss of functionality, reduces quality of life, and enhances morbidity and mortality [1]. The disease course varies greatly between patients; some patients have a mild disease course although in the majority of patients, the disease leads to progressive joint destruction and disability. Besides articular symptoms, RA can be associated with extra-articular features [2].

Among those extra-articular features are cardiovascular diseases, including pericarditis, cardiomyopathy, myocarditis, cardiac amyloidosis, coronary vasculitis, arrhythmias, valve diseases and, most importantly, congestive heart failure (CHF) and ischemic heart disease [3]. When compared with the general population, RA is associated with an increased mortality, the majority of which is originating from cardiovascular diseases. Patients with RA have an approximately two-fold higher incidence of CHF

compared with the general population [4]. CHF is an independent risk factor for mortality in RA patients and is responsible for one in eight deaths of patients with RA [5].

Heart failure is the result of either systolic or diastolic dysfunction or both; left ventricular diastolic dysfunction (LVDD) encompasses mechanical abnormalities involving decreased distensibility, impaired relaxation, and abnormal diastolic filling of the left ventricle, irrespective of the ejection fraction [6]. Diastolic dysfunction has been also associated with diabetes mellitus, coronary artery disease, hypertension, and obesity [7].

The importance of diastolic dysfunction lies in the fact that it may serve as a precursor to systolic and diastolic

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CHF and also may cause morbidity and mortality on its own. It was reported that a number of patients with RA in whom no clinical cardiac abnormalities could be detected having diastolic dysfunction as detected by echocardiography suggests a subclinical myocardial involvement [8].

Diastolic dysfunction is an echocardiographic diagnosis made via transthoracic echocardiography, and cannot be made clinically [9]. Doppler echocardiography is a sensitive and noninvasive method of detecting cardiac abnormalities and systolic and/or diastolic function. Early identification of diastolic dysfunction in asymptomatic patients by echocardiography may provide an opportunity to manage the underlying etiology appropriately to prevent its progression to diastolic heart failure [10].

The higher incidence of CHF in RA necessitates the research of its precursor forms and preclinical assessment, and therefore the importance of studying diastolic dysfunction in patients with RA. The aim of this study was to determine the prevalence of LVDD in patients with RA with no history of heart diseases, and to study its association with other RA disease parameters.

Patients and methods

Patients

This is a cross-sectional study conducted on 75 RA patients who fulfilled the 2010 American College of Rheumatology and European League Against Rheumatism classification criteria for RA [11]. The patients were attending the Rheumatology Outpatient Clinic at Beni-Suef University Hospital, Egypt. Their age ranged from 20 to 45 years and disease duration ranged from 1 to 21 years. The patients were matched by age and sex to 38 healthy participants who served as a control group. The patients were studied from February 2018 through December 2018. The study was carried out with the approval of local ethics committee and in accordance with the national law and the Helsinki Declaration of 1975. Informed consent was obtained from all patients.

Exclusion criteria

None of the patients included in this study had evidence of cardiac disease as assessed by history, physical examination, and standard 12-lead ECG. They had no evidence of hypertension, ischemic heart disease, rheumatic heart disease, or any valvular heart disease, ventricular hypertrophy or pathological Q wave or arrhythmia on ECG. Other

diseases like diabetes mellitus, renal insufficiency, hyperlipidemia, smoking, pregnancy, obesity (BMI \geq 30) had been also excluded.

Clinical evaluation

All patients were subjected to full medical history taking and clinical examination. Each patient underwent clinical examination by a rheumatologist and cardiac assessment by a cardiologist. Weight and height were also determined to calculate BMI. Pain intensity was assessed using visual analog scale [12]. Joint tenderness was performed using Ritchie Articular index [13].

Rheumatoid arthritis activity

Current RA disease activity was measured using 28 Joint Disease Activity Score (DAS28) [14]. DAS28 is a composite score that consists of swollen and tender joint counts (0–28), erythrocyte sedimentation rate, and patient-assessed global score (0–100). A score above 5.1 means high disease activity, whereas a score below 3.2 indicates low disease activity.

Rheumatoid arthritis disability

Assessment of RA disability was done using the Arabic Version of the Health Assessment Questionnaire Disability Index [15].

Investigations

Complete blood count, first hour erythrocyte sedimentation rate (Westergren) [16], C-reactive protein, serum aspartate aminotransferase and alanine aminotransferase, serum creatinine and blood urea, rheumatoid factor by latex fixation test, anticyclic citrullinated peptide antibodies, cholesterol, high-density lipoprotein, low-density lipoprotein, fasting and postprandial blood sugar, chest radiography and hand radiography were done for all patients.

ECG

ECG was done to all patients and controls to exclude arrhythmias, chamber enlargement, and pathological Q wave, S-T and T wave changes, and QRS complex.

Echocardiography and Doppler ultrasound

The above tests were performed for all patients and controls according to the recommendations of the American Society of Echocardiography [17]. Echocardiography was performed by a trained cardiologist who was blinded to the clinical status of both groups and used the same echocardiographic instrument throughout the study. Echocardiography was performed to assess the flow pattern of the heart valves. All M-mode, two-dimensional Doppler

echocardiography measurements were averaged from at least three consecutive cardiac cycles. Assessment of the following parameters was done:

- (1) The pericardial fluid and thickness.
- (2) Chamber dimensions.
- (3) Systolic parameters of the left ventricle such as the left ventricular end systolic diameter, left ventricular end diastolic diameter, and ejection fraction were calculated using the M-Mode by assessment of fractional shortening, left ventricular posterior wall thickness, and septal wall thickness.
- (4) Diastolic parameters of the left ventricle such as peak early transmitral filling velocity (E wave in m/s), peak atrial filling velocity or late transmitral filling velocity (A wave in m/s), E/A ratio (usually >1 in young normal participants), E acceleration time, E deceleration time and E duration (in ms), A acceleration time, and deceleration time (in ms).

According to the E/A ratio and the deceleration time, the diastolic dysfunction was categorized into four categories [18]:

- (1) Grade I diastolic dysfunction (mild): impaired relaxation.
- (2) Grade II diastolic dysfunction (moderate): pseudonormalization.
- (3) Grade III diastolic dysfunction (severe, reversible): reversible restrictive pattern.
- (4) Grade IV diastolic dysfunction (severe, irreversible): irreversible restrictive pattern.

Statistical analysis

Data were analyzed by the statistical package for the social sciences (version 20.0 for Windows, SPSS Inc., Chicago, IL). Differences in frequencies were analyzed by Fisher's exact test as appropriate. Student's *t*-test was used to compare the difference between two group means in interval and ordinal variables. Associations between interval, ordinal, and dichotomous variables were tested by Pearson's product moment correlation coefficients (*r*). Two-tailed tests were used throughout, with statistical significance set at the conventional 95% level.

Results

Demographic data and clinical features

Among the 75 studied patients, there were 58 (77.3%) women and 17 (22.7%) males. The mean age of RA patients was 33.4±7.5 (ranging from 20 to 45 years), the

Table 1 Disease characteristics of rheumatoid arthritis patients

	Range	Mean±SD
Age	20–45	33.4±7.5
Disease duration	1–21	7.2±5.7
Age at onset [n (%)]		
10–19	9 (18)	
20–29	23 (46)	
30–39	17 (34)	
40–49	1 (2)	
DAS28	2.1–5.6	3.8±1.2
HAQ	0.12–2.87	0.97±0.7

DAS28, 28 Joint Disease Activity Score; HAQ, Health Assessment Questionnaire.

mean duration of illness was 7.2±5.7 (ranging from 1–21 years) with 72% seropositive for rheumatoid factor and 20% seropositive for anticyclic citrullinated peptide antibody. The mean DAS28 was 3.8±1.2 (ranging from 2.1–5.6), whereas the mean Health Assessment Questionnaire score was 0.97±0.7 (ranging from 0.12 to 2.87) (Table 1). At the time of the study, 36 (48%) patients were receiving methotrexate, 30 (40%) patients were on antimalarials, and 14 (18.7%) patients were receiving corticosteroids, whereas 12 (16%) patients were on biologic therapy. Combination between methotrexate and antimalarials was the most common, being detected in 23 (30.7%) patients.

Among the 38 healthy controls, there were nine (23.7%) men and 29 (76.3%) women; their age ranged from 20 to 45 years with a mean of 32.7±7.8 years. Both patient and control groups were matched for age and sex.

Prevalence of diastolic dysfunction in rheumatoid arthritis patients and controls

Diastolic dysfunction was significantly more common in the RA group being detected in 28 (37.3%) patients compared with four (10.5%) healthy participants in the control group ($P<0.05$). Among the 37.3% RA patients diagnosed with diastolic dysfunction, 18 (24%) patients had mild diastolic dysfunction with the remaining 10 (13.3%) having moderate diastolic dysfunction. However, in the control group, four (10.5%) patients only had mild diastolic dysfunction with no reported cases of moderate or severe diastolic dysfunction.

Our finding of increased prevalence of diastolic dysfunction in RA patients was further supported by other echocardiographic findings. RA patients had a significantly higher left atrium diameter compared with non-RA participants ($P<0.01$). The E wave

Table 2 Echocardiographic findings in rheumatoid arthritis patients and controls

	Patients (n=75)	Control (n=38)	P value
Left atrium diameter (cm)	3.6±0.2	3.1±0.2	0.01*
LVEDD (cm)	4.5±0.4	4.7±0.3	0.63
LVEF (%)	66.8±4.1	66.2±3.9	0.83
E wave (m/s)	0.6±0.4	0.8±0.4	0.003**
A wave (m/s)	0.7±0.3	0.6±0.3	0.61
E/A ratio	1.1±0.4	1.4±0.5	0.002*
Valve affection [n (%)]			
Yes	10 (13.3)	0 (0)	0.05**
No	65 (86.7)	38 (100)	

LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction. * $P<0.05$, significant difference. ** $P<0.01$, significant difference.

Table 3 Correlations between diastolic dysfunction in rheumatoid arthritis patients with different disease characteristics

	Diastolic dysfunction	
	r	P
Age (years)	0.12	0.55
Age at onset	0.03	0.88
Sex	0.08	0.68
BMI	0.18	0.32
Disease duration	0.41*	0.01
Articular index	0.06	0.74
Swollen joints	0.17	0.35
DAS28	0.43*	0.01
HAQ	0.09	0.62
Methotrexate	0.34	0.06

DAS28, 28 Joint Disease Activity Score; HAQ, Health Assessment Questionnaire. * $P<0.05$, significant difference.

and E/A ratio were both significantly lower in the RA group than the control group ($P<0.01$). In addition, 10 (13.3%) of the RA patients had valvular affection in the form of mitral regurgitation, whereas none of the control group had any (Table 2).

Correlation between diastolic dysfunction and rheumatoid arthritis disease parameters

The presence of diastolic dysfunction in RA patients was statistically significantly positively correlated with disease duration ($r=0.41$, $P<0.05$) and disease activity ($r=0.43$, $P<0.05$) (Table 3). The presence of diastolic dysfunction was statistically significant higher in patients with severe and moderate disease activity than those with mild activity ($P<0.05$). However, the difference between different grades of disease disability regarding the presence of diastolic dysfunction was statistically insignificant (Table 4).

Discussion

Seventy-five Egyptian RA patients satisfying the 2010 American College of Rheumatology and European League against Rheumatism classification criteria for RA [11] and 38 controls were recruited for this study.

Table 4 Diastolic dysfunction in rheumatoid arthritis patients with different grades of disease activity and disability

	Total	DD [n (%)]	P value
DAS28			
Mild	30	3 (10)	0.001**
Moderate	33	15 (45.4)	
Severe	12	10 (83.3)	
HAQ			
Mild	34	14 (41.2)	0.6
Moderate	38	14 (36.8)	
Severe	3	0 (0)	

DD, diastolic dysfunction; DAS28, 28 Joint Disease Activity Score; HAQ, Health Assessment Questionnaire. ** $P<0.01$, significant difference.

Diagnosis of LVDD was based on Doppler echocardiography. The aim of the study was to evaluate the LVDD as an early predictor of asymptomatic cardiac involvement in patients with RA detected by Doppler echocardiography and to correlate diastolic function in those patients with different RA disease characteristics.

The main limitation of this study was the nature of a cross-sectional study which may limit the types of conclusions that can be drawn, as these observations are associations and not necessarily causal.

In our study, diastolic dysfunction was detected in 28 (37.2%) of RA patients and in four (10.5%) of the control group, in accordance with the study by Montecucco *et al.* [8], in which impairment of diastolic dysfunction was reported in 38.9% of RA and in 25.9% of controls in a study of 54 RA patients and 54 healthy participants [8]. Another study by Crowsen *et al.* [19] had determined the presence of diastolic dysfunction in 26.5% and in 21.7% of non-RA.

Several studies have reported an association between RA and features of impaired diastolic ventricular function, as reviewed by Giles *et al.* [20] using Doppler determination of transmitral flow velocity Alterations of the E/A ratio

have been demonstrated for RA patients compared with controls in several studies [8,21–26]. Similar to our study, many studies have confirmed the high presence of diastolic dysfunction in RA patients and lower impairment of E/A ratio compared with the control group. Arslan *et al.* [27] had conducted a study on 52 RA patients and 47 normal persons to assess the left ventricular diastolic function by assessment of transmitral flow and tissue Doppler imaging, and they observed that E/A ratio was significantly statistically lower in RA patients than in controls. Another study conducted by Udayakumar *et al.* [28] studied 45 RA patients and confirmed a high frequency of LVDD in patients with RA without evident cardiovascular disease when compared with controls.

In contrast, other studies showed no statistically significant difference between RA patients and control population as regards the prevalence of diastolic dysfunction [26,29–31].

The main explanation of this variation in diastolic dysfunction presence might be due to the fact that some of the studies perhaps use different techniques to assess diastolic dysfunction. Observer bias should be considered as most studies did not specify if the echocardiography was blinded or not. Several factors may confound the reported findings in the selected studies. The E/A ratio was by far the most frequently used echocardiographic parameter to assess diastolic function in the studies. Hence, we used this variable in our pooled analysis. In clinical practice, assessment of diastolic function is based on a combination of parameters such as propagation velocity and intraventricular dispersion of E wave velocity. This may limit the generalization of our findings.

In addition, some studies did not exclude associated cardiac diseases in their studies, whereas others did. Notably, all of our RA patients have no symptoms or signs suggestive of any cardiac disease. Isolated diastolic dysfunction has been previously associated with a marked increase in mortality in the general population [32,33]. Hence, the increased prevalence of isolated diastolic dysfunction in RA may have implications on excess mortality in RA patients [34]. For this reason, primary diastolic dysfunction is an important cause of heart failure, as it is often a silent alteration preceding systolic dysfunction. So, knowledge of this complication in patients with RA without clinically evident cardiac disease may be important to improve patient survival. In our study, duration of RA disease was strongly associated with diastolic dysfunction, although, some other studies did

not suggest such a link [35]. Similar to our finding, a correlation between diastolic dysfunction and disease duration in patients with RA had also been reported in other study [36]. Sonkusare *et al.* [37] studied 35 RA patients versus 25 controls and they concluded that diastolic dysfunction may develop especially in RA patients with disease duration of more than 5 years. This actually may reflect a chronic subclinical myocardial process leading to impairment of myocardial function [34].

Our study showed a significant positive correlation between LVDD and disease activity assessed by the DAS28 score. This finding was in agreement with the study of Carlos *et al.* [38] who also used DAS28 in assessment of activity. Another study by Targońska-Stepniak *et al.* [39] reported a significant correlation between diastolic dysfunction and the activity of RA. This could be explained by the fact that active disease may be associated with interstitial fibrosis and diminished left ventricular compliance that ends in diastolic dysfunction.

Conclusion

This study highlights that RA patients are more susceptible to cardiac complications more than normal patients. Therefore, routine screening of RA patients with Doppler echocardiography may detect subclinical cardiac involvement and corrective measures could be done before clinically evident heart failure ensues. Knowledge of this complication in patients with RA without clinically evident cardiac disease may be important to improve patient survival.

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Conflicts of interest

There are no conflicts of interest.

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