

DIASTOLIC DYSFUNCTION IN RHEUMATOID ARTHRITISR. Sonkusare¹, S. S. Nelson²**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown origin with a heterogeneous clinical picture. The characteristic feature of Rheumatoid arthritis is persistent inflammatory synovitis. Inflammation, characteristic of active RA, likely plays a major role in cardiovascular disease. Cardiac involvement (pericardial, myocardial, endocardial) is known in patients of Rheumatoid arthritis. Cardiac failure is the result of either systolic or diastolic dysfunction, or both. Some echocardiographic studies have demonstrated disturbances in left ventricular diastolic function of RA patients. **OBJECTIVES:** To study the clinical profile and echocardiographic abnormalities in RA patients. To find out the incidence of diastolic dysfunction in RA. To study the correlation between E/A ratio in RA. **METHOD:** The study is based on the echocardiographic outcome of 35 cases of RA and 25 controls attending the Rheumatology clinic or admitted in medicine wards. **RESULTS:** Incidence of diastolic dysfunction in our series was 48.58% among cases. Diastolic dysfunction was present in patients more than forty years of age and disease duration more than five years. 68.58% (24 out of 35) cases had positive family history of Rheumatoid Arthritis and out of them 66.66% (16/24) had diastolic dysfunction. There was a higher incidence of diastolic dysfunction (78.94%) in patients with a higher joint count (more than sixteen). **CONCLUSIONS:** Diastolic dysfunction may develop especially in RA patients with disease duration of more than 5 years. A family history of RA and a higher joint count are risk factors for the development of diastolic dysfunction in patients of RA.

KEYWORDS: RA: Rheumatoid Arthritis, E: Early diastolic flow velocity, A: Late diastolic flow velocity, ECG: Electrocardiogram, LVEDD: Left ventricular end diastolic dimension, LVESD: Left ventricular end systolic dimension EF: Ejection fraction, LA: Left atrial diameter, AR: Aortic root diameter, IVS: Inter ventricular septum, LVPW: Left ventricular posterior wall, CCF: Congestive cardiac failure, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate.

INTRODUCTION: Rheumatoid arthritis is a chronic multisystem disease of unknown origin with a heterogeneous clinical picture. The characteristic feature of Rheumatoid arthritis is persistent inflammatory synovitis usually involving peripheral joints in a systemic distribution. The potential of synovial inflammation to cause cartilage damage, bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Inflammation, characteristic of active RA, likely plays a major role in cardiovascular disease.¹

Cardiac involvement (pericardial, myocardial, endocardial) is known in patients of Rheumatoid arthritis. Long term survival of patients with Rheumatoid Arthritis (RA) is shorter compared with the general population or control subjects without RA.² Among the different causes of death, increased mortality from heart disease with high prevalence of congestive heart failure was reported in many studies.^{2,3} Necropsy studies showed a high incidence of pericardial, myocardial and endocardial involvement in RA patients.⁴

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However, cardiac disease is often clinically silent and is rarely a severe life threatening complication in RA. Cardiac failure is the result of either systolic or diastolic dysfunction, or both. Left ventricular (LV) diastolic dysfunction is usually attributable to common structural abnormalities such as hypertrophy or interstitial fibrosis and impaired myocyte relaxation resulting from ischemia.⁵

Some echocardiographic studies have demonstrated disturbances in left ventricular diastolic function of RA patients.⁶ The reason for these abnormalities is not yet fully understood. Cardiovascular mortality has been identified as the underlying cause of a substantial proportion of deaths among patients with RA, with a standardized mortality ratio that ranges from 1.3 to 2.4 in most studies.⁷⁻⁹ Recent reports have also described an increased risk of congestive heart failure (CHF) as an important contributory cause of Cardiovascular-associated death.

Systolic and diastolic functions of the left ventricle have been frequently studied in adults with Rheumatoid arthritis. Clinical manifestations are usually mild and myocardial involvement may present as congestive heart failure. Heart failure syndrome, however, may also occur in patients with preserved left ventricular ejection fraction but with abnormalities in left ventricular diastolic function. Such a Heart failure syndrome (diastolic heart failure) is caused by left ventricular diastolic dysfunction, leading to increased resistance to left ventricular filling and eventually resulting in Heart failure syndrome. Certain conditions such as ischemia, left ventricular hypertrophy, hypertension and aortic stenosis predispose to diastolic dysfunction¹⁰. Impaired ventricular relaxation and increased ventricular stiffness are mechanisms by which these conditions lead to diastolic dysfunction and subsequently to diastolic heart failure.¹¹ Diastolic dysfunction itself, without clinical evidence of heart failure has been associated with increased all cause mortality and increases risk of developing congestive heart failure. Thus diastolic dysfunction may be viewed as precursor of diastolic heart failure.

AIMS AND OBJECTIVES:

1. To study the clinical profile of Rheumatoid Arthritis.
2. To study the Echocardiographic abnormalities in Rheumatoid Arthritis.
3. To find out the incidence of diastolic dysfunction in Rheumatoid Arthritis.
4. To study the correlation between E/A ratio in Rheumatoid Arthritis.

MATERIAL AND METHODS: The case control study was carried in 2009 in the Rheumatology clinic and cases admitted, in the Department of Medicine, N. S. C. B. Medical College and Hospital Jabalpur, M.P.

INCLUSION CRITERIA:

1. Rheumatoid Arthritis cases who are Rheumatoid Factor positive and fulfill at least four American college of Rheumatology (ACR) criteria of Rheumatoid Arthritis.
2. Rheumatoid Arthritis cases or controls that do not have any symptomatic cardiac illness.

EXCLUSION CRITERIA:

1. Rheumatoid Factor positive cases who do not fulfill four ACR criteria.
2. Rheumatoid Arthritis cases or controls that have co-existing cardiac disease.

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Patient's Characteristics: We selected 35 cases [8 Male, 27 Female] from a patient population aged [43.97±13.15] years referred to our rheumatology outpatient clinic. All patients were in sinus rhythm. All the cases were informed of the purpose of the study and gave their consent. The study was also approved by ethics committee of our institute.

All cases fulfilled the revised ACR criteria 1987 for the diagnosis of RA, and had no symptoms of cardiac disease.

Patient evaluation included a complete history and musculoskeletal examination. Twenty eight joint counts was done in all RA patients.

Patients with history of Rheumatic heart disease, primary cardiomyopathy, congenital heart disease, myocardial, endocardial, or valvular heart disease, coronary artery disease or arrhythmia, those with small echo window and poor image quality, history of diabetes, chronic lung disease, trauma, arterial hypotension, arterial hypertension other connective tissue disorder (congenital or inflammatory) were excluded from study.

Patients had routine laboratory studies. Blood pressure was measured using a mercury sphygmomanometer on three visits on at least one week intervals. The average of the last set of reading was used as clinical measurements.

As a control group [14 Male, 11 Female] with average age of [40.76± 11.64] years was selected randomly from healthy population who belonged to the same age and sex and had negative Rheumatoid Factor report, and were without any cardiovascular disease.

All subjects underwent a complete echocardiographic examination. However, RA patients discontinued any therapy for a period of at least 10 days before echocardiographic examination. Moreover no patient had received steroids in the last 4 months.

Examination: Attention was focused on body habitus, height, weight, pulse, blood pressure.

Systemic Examination was done according to standard clinical practice.

Local examination:

Total number of tender and swollen joints were counted out of 28 joints and disease activity was calculated (Disease activity score 28).

Investigation:

1. Rheumatoid Factor: This investigation was performed by latex agglutination test.
2. Complete hemogram, lipid profile.
3. ESR: After a 4 hr. fasting blood was collected for erythrocyte sedimentation rate (ESR) [according to westergren method (mm/h)].
4. X-Rays: X-Ray of both hands and wrists were done to find out erosions in bone.
5. ECG: A complete 12 leads electrocardiography was done all case and control group, to rule out any ischemic disease, arrhythmia or conduction block.
6. Echocardiography: Echocardiographic examinations all patients underwent a complete transthoracic echocardiography examination: two-dimensional echo was done by BPL US 9101 echocardiographic machine. Color Doppler was done by Seimens 5, 500 with a P 4- 2 ultrasound transducer.

The following structures and factors were assessed during the echocardiographic examination: left atrial end-systolic diameter (LA), left ventricular end-diastolic diameter (LVEDD),

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right ventricular end-diastolic diameter (RVEDD), interventricular septum end-diastolic thickness (IVSEDT), left ventricular posterior wall end-diastolic thickness (LVPWEDT), aortic root diameter (AO), ejection fraction (EF). In M-mode technology, the end-systolic antero-posterior diameter in the parasternal projection of the left side of a patient is accepted as the size of the left atrium (LA). The end-diastolic antero-posterior diameter in the parasternal projection of the left side of a patient is accepted as the size of the left ventricle (LV), right ventricle (RV), thickness of an interventricular septum (IVS), left ventricle posterior wall (LVPW) and aortic root diameter (AO).

The ejection fraction was calculated as follows: $\text{LV diastolic volume} - \text{LV systolic volume} / \text{LV diastolic volume} \times 100$.

The cardiac chamber dimensions and wall thickness was measured by M mode echocardiography. All recordings and measurements were performed according to the recommendations of the Committee for M-mode standardization of the American Society of Echocardiography.

Color Doppler echocardiography was used to obtain transmitral flow determined from the apical four chamber view. To record transmitral flow the sample volume was carefully positioned at the tip of the leaflets of mitral valve. The following variables were evaluated as parameters of left ventricular filling: peak of early diastolic (E) and late diastolic (A) flow velocity, E/A ratio. Doppler sample volume was placed between the flow velocity, E/A ratio. Doppler sample volume was placed between the mitral inflow and left ventricular outflow and transmitral and transaortic flow.

Diastolic dysfunction was defined by the presence of one of the following patterns (for the inclusion of a patient in a certain pattern all the criteria for that specific pattern should be fulfilled).

1. Impaired relaxation pattern if B/A ratio was <1.1 ,
2. Pseudo normalized pattern if B/A ratio was between 1.1 to 1.5,
3. Restrictive pattern was considered to be present if B/A ratio was >1.5 , (112).

OBSERVATION: In this case-control study 35 sero-positive cases of Rheumatoid Arthritis were compared echocardiographically to 25 controls.

Maximum number of Cases 19 (54.3%) belonged to 40-59 Yrs. group ($P>0.05$).

20 cases (57.1%) had duration of illness of more than 5 years.

S.No.	Features	Case	Control	P Value
1.	No. of Cases	35	25	$P>0.05$
2.	M/F	8/27	14/11	$P>0.05$
3.	Heart rate (Beat/min)	8.34 ± 13.14	82.32 ± 12.38	$P>0.05$
4.	SBP (mmHg)	128.63 ± 9.91	126.40 ± 8.86	$P>0.05$
5.	DBP (mmHg)	77.08 ± 5.55	76.81 ± 3.61	$P>0.05$
6.	Mean Duration	5.78 ± 3.29	-	-
7.	Mean Age	43.97 ± 13.16	40.76 ± 11.65	$P>0.05$

TABLE -1: DISTRIBUTION OF STUDY GROUP (CASES AND CONTROL)

The mean duration of disease was 5.78 ± 3.29 years in the RA group. There were no significant differences in age, heart rate, systolic and diastolic blood pressure between RA patients and controls.

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S. No.	Echo and Color Doppler	Cases (n-35)	Control (n=25)
1.	Left ventricular diastolic dysfunction	17 (48.58%)	2 (8%)
2.	Normal study	18 (51.42%)	23 (92%)
	Total	35	25

TABLE -2: INCIDENCE OF LEFT VENTRICULAR DIATOLIC DYSFUNCTION IN CASES AND CONTROL

$$X^2 = 2.57; P > 0.05$$

Incidence of diastolic dysfunction in our series and control was 48.58% (17/35 cases) and 8% (2/25 controls) respectively.

S. No.	Family History of RA	Diastolic dysfunctions		Total
		Present (%)	Absent (%)	
1.	Present	16 (66.66%)	8 (33.34%)	24 (68.58%)
2.	Absent	1 (9.09%)	10 (90.90%)	11 (31.42%)
	Total	17	18	35

TABLE -3: ASSOCIATION BETWEEN FAMILY HISTORY OF RA AND DIASTOLIC DYSFUNCTION IN STUDIED CASES

$$X^2 = 10.01; P > 0.01$$

There was a significant association of family history of RA and diastolic dysfunction. 68.58% (24 out of 35) cases had positive family history of Rheumatoid Arthritis and out of them 66.66% (16/24) had diastolic dysfunction.

S. No.	No. Joints	Diastolic dysfunction		Total
		Present	Absent	
1.	0-8	1	2	3
2.	9-16	1	12	13
3.	>16	15	4	19
	Total	17	18	35

TABLE -4: ASSOCIATION BETWEEN NUMBER OF JOINTS INVOLVED AND DIASTOLIC DYSFUNCTION IN STUDIED CASES

$$X^2 = 15.99; P > 0.01$$

A total of 28 joints were counted. There was a significant association between joint involvement and diastolic dysfunction. Maximum number of cases 19 out of 35 cases (54.28%) had more than 16 joints involved and out of them 15 cases (78.94%) had diastolic dysfunction.

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Echo Parameter.	RA patients (Mean ±SD)	Control Group (Mean ±SD)	P Value
L.VESD (mm)	46.60±2.56	46.92 ± 2.23	P>0.05
L.VESD (mm)	33.37 ± 2.55	33.08 ± 1.38	P>0.05
LA (mm)	35.20 ± 2.59	28.88±3.15	P<0.05*
AOROOT (cm)	2.79 ± 0.41	2.7880 ± 0.44	P>0.05
IVS (cm)	1.04 ± 0.15	1.0040 ± 0.08	P>0.05
LVPW (cm)	0.99 ±0.16	.9840 ± 0.15	P>0.05
EF (%)	62.86% ± 6.86	63.96 ± 6.426	P>0.05

TABLE -5: ECHOCARDIORAPHIC MEASUREMENTS IN RA CASES AND CONTROLS

* P<0.05 Significant

In this table left atrial diameter was significantly increased in cases as compared to controls.

Echo Parameter.	RA patients (Mean ±SD)	Control Group (Mean ±SD)	P Value
E(m/sec)	0.84 ± 0.13	0.84 ± 0.05	P>0.05
A (m/sec)	0.81 ± 0.14	0.73 ± 0.14	P<0.05*
E/A	1.03 ± 0.21	1.15 ± 0.22	P<.05*

TABLE -6: COLOUR DOPPLER MEASUREMENTS IN RA CASES AND CONTROLS

*P<0.05 significant

Left diastolic flow velocity was significantly higher and E/A ratio was significantly lower in cases

Parameters	Duration of RA			AGE		
	<5yrs	>5yrs	P value	<40yrs	>40yrs	P value
LVEDD (mm)	46.2±2.2	46±2.8	p>0.05	45.92±3.26	46.96±2.10	p>0.05
LVESD (mm)	33.3±2.2	33.5±2.8	p>0.05	33.08±2.54	33.52±2.59	p>0.05
LA (mm)	35.3±3.0	35.1±2.3	p>0.05	33.50±2.35	35.04±2.74	p>0.05
Aortic root (cm)	2.9±0.5	2.7±0.4	p>0.05	2.82±0.48	2.77±0.39	p>0.05
IVS (mm)	1.0±0.1	1.1±0.2	p>0.05	0.97±0.13	1.07±0.15	p>0.05
LVPW (cm)	0.9±0.1	1.0±0.2	p>0.05	0.88±0.11	1.05±0.15	P<0.05
EF (%)	63.9±5.4	62.1±7.8	p>0.05	63.22±7.63	62.17±5.32	p>0.05
E (m/s)	1.9±0.2	0.84±0.1	p>0.05	0.90±0.13	0.85±0.11	P<0.05
A (m/s)	0.7±0.1	0.9±0.1	P<0.05	0.73±0.11	0.9±0.1	P<0.05
E/A	1.2±0.4	0.94±0.1	P<0.05	1.2±0.4	0.94±0.1	P<0.05

TABLE -7: Comparison between Echocardiographic measurement values and duration of RA and Age of patients

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Late diastolic flow velocity was significantly higher, and E/A ratio was significantly less than 1 in cases those had longer disease duration (more than 5 years). While left ventricular posterior wall, Late diastolic flow velocity were significantly higher, and early flow velocity significantly low and E/A ratio were significantly less than 1 in cases those who were more than 40 years age.

DISCUSSION: In this case-control study 35 sero-positive cases of Rheumatoid Arthritis were compared echocardiographically to 25 controls. All subjects were free from cardiovascular disease. The maximum number of cases 19 (54.3%) belonged to 40-59 age group. Mean age of cases in this study was 44.97 ± 13.16 with mean duration of disease 5.78 years. There were female predominance in our study female to male ratio was 3.37:1.

When we categorized the patients into two groups; those with early RA (the disease duration of less than 5 years) and those with late RA (the disease duration of more than 5 years) maximum number of cases 57.1% (20 cases) had duration of illness more than 5 years. Similarly in the study by Irfan Yovasoglu et al 2007¹² they found significant differences between the two groups in mitral E/A ratio ($p = 0.009$).

In our study 68.58% (24 out of 35) cases had positive family history of Rheumatoid Arthritis out of them 66.67% (16 out of 24) cases had diastolic dysfunction. This finding was strongly significant (p value < 0.01). This showed that chances of diastolic dysfunction may be more in those cases who had positive family history of Rheumatoid Arthritis.

In Udayakumar et al 2007¹³ Rheumatoid factor was significantly positive in patients of RA with left ventricular diastolic dysfunction (89.5% versus 42.3%; $p = 0.02$).

In our study left ventricular end diastolic dimension and left ventricular end systolic dimension of cases and controls were (mean \pm SD) 46.60 ± 2.55 , 33.37 ± 2.55 and 46.92 ± 2.23 , 33.08 ± 1.38 respectively which were within normal limit. Ejection fraction was also within normal limit in cases and controls (mean \pm SD) 62.86 ± 6.86 and 63.96 ± 6.42 . which showed that systolic function was within normal limit.

The overall incidence of diastolic dysfunction in our study was 48.58 % (17 out of 35), while in Udayakumar et al 2007,¹³ the incidence of diastolic dysfunction was 42.2% (19 out of 45).

When we divided our cases in two subgroups on the basis of disease duration of less than or more than 5 years, we found diastolic dysfunction significantly in those cases who had disease duration of more than 5 years. The early diastolic flow velocity was low and the late diastolic flow velocity was significantly high 0.84 ± 0.1 (p value > 0.05), 0.9 ± 0.1 (p value < 0.05) respectively. The E/A ratio was significantly less than 1 (mean \pm SD) 0.94 ± 0.1 p value < 0.05 .

While left ventricular posterior wall, late diastolic flow velocity were significantly higher, and early flow velocity significantly low and E/A ratio were significantly less than 1 in those patients who were more than 40 years age.

Significant reduction in various indices of LV diastolic function were present, whereas no differences in LV end diastolic diameter, systolic function and parietal thickness were found in RA patients as compared to controls. In the study by Wislowska et al¹⁴ early diastolic velocity, E was 0.83 ± 0.198 , late velocity, A was 0.76 ± 0.14 and E/A ratio was 1.16 ± 0.33 . Our findings are consistent with Wislowska et al 2008.¹⁴

Same finding were observed by Udayakumar et al 2007¹³ in which E 0.73 ± 0.9 A 0.77 ± 0.12 E/A was 0.98 ± 0.23 . Our finding are also consistent with this study.

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No correlation was found between age and E/A ratio, as well as between disease duration and E/A ratio due to weak sample size.

There were 19 cases in whom maximum number of joints (>24 joints) were involved. Out of them 15 cases had abnormal diastolic function which was highly significant (p value <0.001). This indicates the possibility of diastolic dysfunction to be high in those cases in whom maximum number of joints were involved.

Diastolic dysfunction can be a primary cause for cardiac failure but it may also precede an impairment of left ventricular systolic function. It remains, however, to be proven in prospective studies if diastolic abnormalities in left ventricular function can in long-term cause an increased occurrence and mortality from cardiac failure in patients with RA.

CONCLUSION: Because primary diastolic dysfunction is an important cause of heart failure, as it often is a silent alteration preceding systolic dysfunction¹⁵, knowledge of this complication in patients with RA without clinically evident cardiac disease may be important to improve patient survival. A correlation between diastolic dysfunction and disease duration in active patients with RA has been reported. Diastolic dysfunction may develop especially in patients with disease duration of more than 5 years. RA does not seem to alter cardiac functions at least in the early periods of the disease. A family history of RA and a higher joint count are risk factors for the development of diastolic dysfunction in RA. Better awareness of these subclinical findings and appropriate therapy may help reduce the high incidence of cardiovascular deaths observed in patients with RA. A complete Echocardiography and color doppler examination is necessary in the management of RA patients to reduce cardiovascular morbidity and mortality, especially those having disease duration of more than 5 years.

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