

Prevalence of left ventricular dysfunction in rheumatoid arthritis

A. S. Renjith¹, Vishal Marwaha², N. Aggarwal³, Varghese Koshy⁴, V.K. Singal⁶,
K. V. S. Hari Kumar⁵

¹Department of Medicine, Military Hospital, Srinagar, ²Department of Rheumatology, Amrita University, School of Medicine, Kochi, ³Department of Cardiology, ⁴Endocrinology, Army Hospital (R&R), Delhi, ⁵Department of Rheumatology, Command Hospital, Chandimandir, ⁶Department of Rheumatology, Medanta Hospital, Delhi, India

ABSTRACT

Background: Rheumatoid arthritis (RA) is a polyarticular disorder with many extra-articular features. Cardiovascular disorders, including heart failure (HF), are the leading causes of mortality in RA patients. We studied the prevalence of left ventricular dysfunction (LVD) in patients with RA. **Materials and Methods:** In this cross-sectional study, we evaluated 100 consecutive patients with RA (aged >18 years and duration >1 year) for the presence of LVD. We excluded patients with known cardiac and systemic disorders that may contribute to LVD. LVD is defined by the presence of either left ventricular systolic dysfunction (LVSD) or left ventricular diastolic dysfunction (LVDD), evaluated by the echocardiography. Descriptive statistics and relevant tests were used to analyze the results. **Results:** The study participants ($n = 100$; 80F and 20M) had a mean age of 45 ± 11.8 years, duration of disease 7.4 ± 5.4 years, and disease activity score of 3.5 ± 1.1 . A total of 46 patients had symptoms of HF, but only 14% of them had signs of HF. LVD was seen in 59 (LVSD-4, LVDD-50, and both together in 5) patients, and none of the participants had severe grades of LVSD and LVDD. LVD showed no relation to the age of the patients ($P = 0.186$) and it was more with increasing duration of RA ($P < 0.001$) and higher disease activity ($P = 0.042$). **Conclusion:** LVD is more common in RA patients, which increases the associated morbidity and mortality. Higher threshold is required by the family practitioners to perform a screening echocardiography in long-standing RA patients.

Keywords: Cardiovascular disease, diastolic dysfunction, heart failure, rheumatoid arthritis, systolic dysfunction

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves synovial joints.^[1] In progressive disease, there is destruction of joints due to erosion of the cartilage and bone, leading to joint deformities.^[2] Although the central pathology of RA is limited to the synovium of the diarthrodial joints, many nonarticular organs become involved in chronic cases.^[3] The inflammatory response and the cytokines that drive the synovial pathology are responsible for pathophysiological changes in

the extra-articular tissues.^[4] Nearly 40% of patients with RA have extra-articular features over a lifetime of the disease.^[5] The extra-articular features of RA include cardiac (pericarditis, left ventricular dysfunction (LVD), and pericardial effusion), ocular (scleritis, episcleritis, and scleromalacia perforans), pulmonary (nodules, fibrosis, and pleural effusion), neurological (polyneuropathy and mononeuropathy multiplex), and hematological (anemia, eosinophilia, and thrombocytosis) disorders.^[3] The extra-articular involvement also indicates the progressive and severe nature of the underlying disease, with an increase in the morbidity and mortality.^[6] The mortality rates in patients with RA are 1.5–1.6-fold higher than in the general population.^[7] The cardiovascular disease is the most

Address for correspondence: Dr. K. V. S. Hari Kumar,
Department of Endocrinology, Army Hospital (R&R),
Delhi Cantt, New Delhi - 110 010, India.
E-mail: hariendo@rediffmail.com

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/2249-4863.214431

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How to cite this article: Renjith AS, Marwaha V, Aggarwal N, Koshy V, Singal VK, Kumar KH. Prevalence of left ventricular dysfunction in rheumatoid arthritis. J Family Med Prim Care 2017;6:622-6.

common attributed cause of death, followed by infections, pulmonary and renal disease.^[8]

Cardiac involvement of RA is in the form of pericarditis, myocarditis, coronary artery disease, heart failure (HF), rheumatoid nodules, atrial fibrillation, and secondary amyloidosis.^[9] The incidence of HF is increased by 2 fold in patients with RA.^[10] The increased cardiovascular morbidity is mediated by the accelerated atherosclerosis, contributed by the inflammatory cytokines.^[11] However, the increased risk of HF is not explained completely by the traditional risk factors. The etiopathogenetic mechanisms responsible for HF in RA include ischemic heart disease, inflammatory mediators, antirheumatic drug therapy, and amyloidosis.^[12] Previous studies from developed countries have shown an increased rate of death attributed to HF in RA.^[13] Indian patients with RA present late and have higher morbidity when compared with the Western population.^[14] The data pertaining to HF in RA are scanty from our country.^[15] Hence, we conducted this study to evaluate the presence of LVD in patients with RA. We also studied the relation between LVD with duration and severity of disease in patients with RA.

Materials and Methods

Study details

The present cross-sectional study was undertaken by the department of medicine at a tertiary level care center. We included 100 consecutive patients with RA (age between 18 and 65 years, duration of RA more than 1 year, and received disease-modifying agents for at least 6 months) who attended the rheumatology/medicine outpatient department for a regular follow-up visit. We excluded patients with known history of cardiac disorders, diabetes, hypertension, hypothyroidism, Cushing's syndrome, anemia, and severe hepatic or renal dysfunction. A detailed history was taken from all the patients regarding the duration and severity of RA, presence of any comorbidity and symptom of HF. Clinical examination was conducted to look for any sign of HF in the form of gallop rhythm, pedal edema, elevated jugular pulse, presence of third heart sound, and pulmonary rales. Disease activity score-28 (DAS-28) was calculated based on the number of swollen or tender joint count, erythrocyte sedimentation rate (ESR), and subjective assessment of disability.^[16]

Study interventions

Baseline investigations were performed, including hemogram, acute phase reactants (ESR and C-reactive protein), and biochemical parameters including liver and kidney function tests. A chest radiograph and electrocardiogram (ECG) were examined for signs of HF. An echocardiography was done on all patients by a single cardiologist who was blinded to the disease activity of RA. The left ventricular (LV) systolic function was assessed using the modified Simpson's method of assessing the LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV).^[17] The stroke volume (SV) is the difference between LVEDV and LVESV, and LV ejection fraction (LVEF) was calculated as the ratio between the SV and LVEDV, expressed as a percentage. LV diastolic function was assessed by obtaining transmitral flow from the apical four-chamber view. The sample volume was positioned at the tip of the leaflets of the mitral valve to record transmitral flow. The following variables were examined as parameters of LV filling: peak of early (E) and late (or atrial) diastolic (A) flow velocity, E/A ratio, and deceleration time (DT).

Definitions

RA was diagnosed if a patient meets at least four of seven criteria based on the 1987 ACR guidelines, and criteria number 1–4 should have been present for at least 6 weeks.^[18] LVD is indicated by the presence of either LV systolic dysfunction (LVSD) or LV diastolic dysfunction (LVDD) or both together. LVSD is defined as the presence of LVEF <55%, and LVDD is defined based on the E/A ratio and DT as per the standard echocardiographic parameters.^[19] The LVSD and LVDD are further graded in severity as shown in Table 1.

Statistical analysis

Descriptive statistics were used to summarize the demographic and echocardiographic findings. For all the measurable data, two group means were compared using Student's *t*-test and analysis of variance for more than two groups. The degrees of association between various measurable data were calculated using Spearman's coefficient of correlation. We used Chi-square test or Fisher's exact test for all the categorical variables. *P* < 0.05 was considered statistically significant, and all the tests were done using the GraphPad Prism Software, Version 6 (GraphPad Software, San Diego, CA, USA).

Table 1: Grading of left ventricular systolic and diastolic dysfunction

LV systolic dysfunction		Grade	LV diastolic dysfunction	
Interpretation	LVEF (%)		Parameters	Interpretation
Normal	>55	0	0.75 < E/A < 1.5, DT > 140 ms	Normal
Borderline	45-55	1	E/A ≤ 0.75	Impaired relaxation
Mild	35-45	2	0.75 < E/A < 1.5, DT > 140 ms	Moderate, pseudonormal
Moderate	25-35	3	E/A > 1.5, DT < 140 ms	Severe, reversible restrictive
Severe	<25	4	E/A > 1.5, DT < 140 ms	Severe, fixed restrictive

LV: Left ventricular; LVEF: Left ventricular ejection fraction; DT: Deceleration time

Results

The study participants ($n = 100$; 80F and 20M) had a mean age of 45 ± 11.8 years, duration of disease of 7.4 ± 5.4 years, and mean DAS score of 3.5 ± 1.1 . The majority of the participants were younger than 50 years and had duration of RA above 5 years. The DAS-28 score was <5.1 in ninety participants showing a relatively well-controlled disease activity in the majority of the participants. A total of 46 patients had symptoms of HF, and dyspnea was the most common symptom. The signs suggestive of HF were evident in only 14% of the patients. Evidence of HF on chest radiograph was present in 5%, and ECG changes suggestive of ventricular dysfunction were observed in 24% of the participants.

LVSD was noted in 9 participants (Grade-1 in 6 and Grade-2 in 3) and LVDD in 55 patients (Grade-1 in 48 and Grade-2 in 7). None of the participants had severe grades of LVSD and LVDD in our study. Together, LVD (presence of either LVSD/LVDD or both) was observed in 59 participants (59%), of which 5 participants had both LVSD and LVDD as shown in Figure 1. Asymptomatic LVD was detected in 11 patients, which was entirely LVDD in nature. Other echocardiographic findings include trivial mitral regurgitation (MR) (eight patients), concentric LVH (eight patients), mild pericardial effusion (three patients), and global hypokinesia (one patient). The presence of LVD showed no relation to the age of the patients ($P = 0.186$) and was higher in males than female patients (85% and 52.5%, respectively). The presence of LVD was more with an increasing duration of RA ($P < 0.001$) and higher DAS-28 score ($P = 0.042$) as shown in Figure 2.

Discussion

Our study showed the prevalence of LVD in almost two-thirds of the RA population of India. Our data also suggest that LVD is higher in long-standing and severe RA patients. The data also suggest that many of these patients are asymptomatic and are picked up by the routine screening echocardiography. Our findings have certain clinical implications for the family

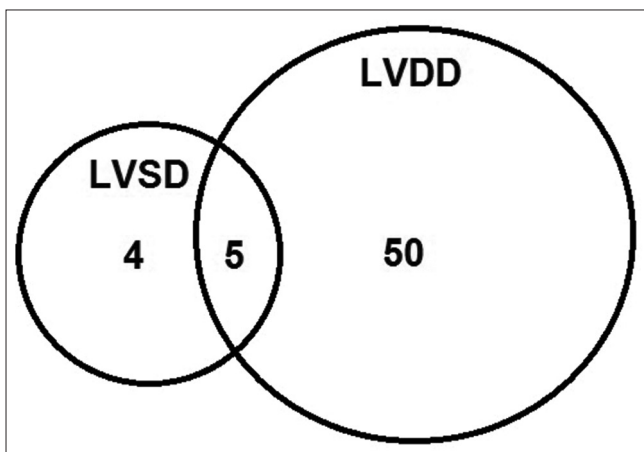


Figure 1: Prevalence of left ventricular dysfunction

practitioners who are involved in the routine care of these patients. First, it is essential to ask for relevant cardiovascular symptoms at every visit to the clinic. Second, the RA patients with disease duration beyond 5 years should be referred for a screening echocardiography to identify the presence of asymptomatic LVD.^[20] Early diagnosis and proper management will go a long way in improving the quality of life of these patients.^[21]

Our study also highlights the increased prevalence of LVD in RA patients despite exclusion of other known causes of the LVD. The overall prevalence of HF in the general population is about 2%, LVSD in 6%, and that of LVDD in 27%.^[22,23] In comparison, our data showed LVSD in 9% and LVDD in 55% of the patients with RA. Previous studies on HF in RA showed conflicting results due to the differences in study population, evaluation methods, and the defining criteria.^[10,14] Bhatia *et al.* showed a higher prevalence of LVSD in RA patients (10.2%) when compared with control population (5.3%).^[24] However, the patients were older than the controls, and they did not exclude patients with known cardiovascular risk factors. Wislowska *et al.* also showed a depressed LVEF in a group of 100 RA patients compared with 100 matched controls.^[25] The RA patients had significant valvular heart disease than the controls (39% vs. 19%), thereby confounding their results. Later studies have failed to

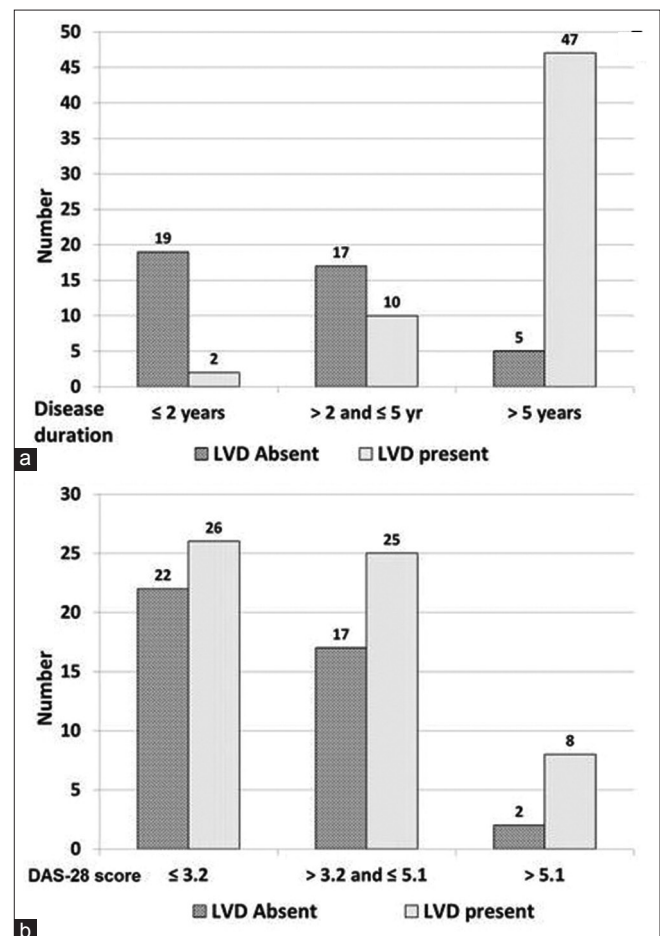


Figure 2: Relation of left ventricular dysfunction according to the disease duration (a) and disease activity score-28 score (b)

establish the above finding, and our study also showed a trivial MR in only 8% of patients. Few authors have shown preserved LV function and increased LV mass in RA patients independent of cardiovascular risk factors.^[26,27]

The association of RA with LVDD has also given conflicting results regarding the prevalence. Liang *et al.* showed LVDD in 31% of RA patients in comparison with general population (26%).^[28] The disease duration and interleukin-6 level were independently associated with LVDD with RA even after adjustment for other cardiovascular risk factors. However, Abdul Muizz *et al.* showed a higher prevalence of LVDD in the control group (51%) than in RA (47%) patients.^[29] Their study showed no significant correlations between the duration of disease, severity, and LVD. Our study showed a higher prevalence of LVDD in patients with RA (57%) compared to the general population (27.3%).^[23] Asymptomatic LVDD is also seen in 11% of the patients, and there was a strong correlation with the duration and severity of RA.

The presence of LVDD with preserved ejection fraction, or isolated diastolic dysfunction, has been previously associated with a marked increase in mortality in the general population.^[30,31] The mechanisms responsible for LVDD in RA include fibrous scarring of the myocardium, myocardial infarction, focal inflammation, vasculitis, and amyloidosis.^[32] The cardiac involvement of RA includes pericardial (pericarditis and pericardial effusion), myocardial (HF, LVD, fibrosis, and amyloidosis), endocardial (Libman–Sacks endocarditis and valvular regurgitation), electrical (arrhythmias, sudden cardiac deaths, atrioventricular blocks, and supraventricular arrhythmia), and vascular (coronary artery disease, vasculitis, and thrombosis) complications.^[9] The strengths of our study include proper echocardiographic assessment of all the patients and close follow-up in a single center. The limitations of our study include small sample size, cross-sectional design, and lack of evaluation of other biochemical markers for HF.

Conclusion

To conclude, a majority of RA patients have LVD, which is associated with the duration and severity of the illness. A close vigil is essential by the family practitioners to screen the RA patients at an appropriate time to identify the underlying LVD. Further large-scale studies with more number of patients are required to confirm the findings observed in our study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? *Curr Opin Rheumatol* 2014;26:64-71.
2. Shiozawa S, Shiozawa K. A review of the histopathological evidence on the pathogenesis of cartilage destruction in rheumatoid arthritis. *Scand J Rheumatol Suppl* 1988;74:65-72.
3. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: Incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003;62:722-7.
4. Giles JT, Fernandes V, Lima JA, Bathon JM. Myocardial dysfunction in rheumatoid arthritis: Epidemiology and pathogenesis. *Arthritis Res Ther* 2005;7:195-207.
5. Davis JM 3rd, Roger VL, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. *Arthritis Rheum* 2008;58:2603-11.
6. Garza-García C, Rocío SS, Orea-Tejeda A, Castillo-Martínez L, Eduardo C, López-Campos JL, *et al.* Risk factors for asymptomatic ventricular dysfunction in rheumatoid arthritis patients. *ISRN Cardiol* 2013;2013:635439.
7. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008;26 5 Suppl 51:S35-61.
8. Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. *J Rheumatol* 2005;32:430-4.
9. Kaplan MJ. Cardiovascular disease in rheumatoid arthritis. *Curr Opin Rheumatol* 2006;18:289-97.
10. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, *et al.* The risk of congestive heart failure in rheumatoid arthritis: A population-based study over 46 years. *Arthritis Rheum* 2005;52:412-20.
11. Ciftci O, Yilmaz S, Topcu S, Caliskan M, Gullu H, Erdogan D, *et al.* Impaired coronary microvascular function and increased intima-media thickness in rheumatoid arthritis. *Atherosclerosis* 2008;198:332-7.
12. Davis JM 3rd, Knutson KL, Strausbauch MA, Crowson CS, Therneau TM, Wettstein PJ, *et al.* A signature of aberrant immune responsiveness identifies myocardial dysfunction in rheumatoid arthritis. *Arthritis Rheum* 2011;63:1497-506.
13. Crowson CS, Nicola PJ, Kremers HM, O'Fallon WM, Therneau TM, Jacobsen SJ, *et al.* How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? *Arthritis Rheum* 2005;52:3039-44.
14. Udayakumar N, Venkatesan S, Rajendiran C. Diastolic function abnormalities in rheumatoid arthritis: Relation with duration of disease. *Singapore Med J* 2007;48:537-42.
15. Bharti BB, Kumar S, Kapoor A, Agarwal A, Mishra R, Sinha N. Assessment of left ventricular systolic and diastolic function in juvenile rheumatoid arthritis. *J Postgrad Med* 2004;50:262-5.
16. Karimifar M, Salesi M, Farajzadegan Z. The association of anti-CCP1 antibodies with disease activity score 28 (DAS-28) in rheumatoid arthritis. *Adv Biomed Res* 2012;1:30.

17. Patel CD, Nadig MR, Kurien S, Barai S, Narang R, Malhotra A. Left ventricular ejection fraction and volumes on rest gated 201Tl perfusion SPECT: Comparison with two-dimensional echocardiography. *Nucl Med Commun* 2006;27:425-9.
18. Berglin E, Dahlqvist SR. Comparison of the 1987 ACR and 2010 ACR/EULAR classification criteria for rheumatoid arthritis in clinical practice: A prospective cohort study. *Scand J Rheumatol* 2013;42:362-8.
19. Vizzardi E, Cavazzana I, Bazzani C, Pezzali N, Ceribelli A, Bonadei I, *et al.* Echocardiographic evaluation of asymptomatic patients affected by rheumatoid arthritis. *J Investig Med* 2012;60:1204-8.
20. Cioffi G, Viapiana O, Ognibeni F, Fracassi E, Giollo A, Adami S, *et al.* Prevalence and factors associated with subclinical left ventricular systolic dysfunction evaluated by mid-wall mechanics in rheumatoid arthritis. *Echocardiography* 2016. doi: 10.1111/echo. 13186.
21. Sharma A, Kaushik R, Kaushik RM, Kakkar R. Echocardiographic evaluation of diastolic dysfunction in rheumatoid arthritis – A case-control study. *Mod Rheumatol* 2015;25:552-7.
22. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.
23. Kuznetsova T, Herbots L, López B, Jin Y, Richart T, Thijs L, *et al.* Prevalence of left ventricular diastolic dysfunction in a general population. *Circ Heart Fail* 2009;2:105-12.
24. Bhatia GS, Sosin MD, Patel JV, Grindulis KA, Khattak FH, Hughes EA, *et al.* Left ventricular systolic dysfunction in rheumatoid disease: An unrecognized burden? *J Am Coll Cardiol* 2006;47:1169-74.
25. Wislowska M, Sypula S, Kowalik I. Echocardiographic findings, 24-hour electrocardiographic Holter monitoring in patients with rheumatoid arthritis according to Steinbrocker's criteria, functional index, value of Waaler-Rose titre and duration of disease. *Clin Rheumatol* 1998;17:369-77.
26. Rudominer RL, Roman MJ, Devereux RB, Paget SA, Schwartz JE, Lockshin MD, *et al.* Independent association of rheumatoid arthritis with increased left ventricular mass but not with reduced ejection fraction. *Arthritis Rheum* 2009;60:22-9.
27. Løgstrup BB, Deibjerg LK, Hedemann-Andersen A, Ellingsen T. Left ventricular function in treatment-naïve early rheumatoid arthritis. *Am J Cardiovasc Dis* 2014;4:79-86.
28. Liang KP, Myasoedova E, Crowson CS, Davis JM, Roger VL, Karon BL, *et al.* Increased prevalence of diastolic dysfunction in rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1665-70.
29. Abdul Muizz AM, Mohd Shahrir MS, Sazliana 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.
30. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, *et al.* Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344-50.
31. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, *et al.* Systolic and diastolic heart failure in the community. *JAMA* 2006;296:2209-16.
32. Aslam F, Bandeali SJ, Khan NA, Alam M. Diastolic dysfunction in rheumatoid arthritis: A meta-analysis and systematic review. *Arthritis Care Res (Hoboken)* 2013;65:534-43.