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ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC DYSFUNCTION IN RHEUMATOID ARTHRITIS PATIENTS

Medicine

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ABSTRACT

Aims : To evaluate left ventricular systolic dysfunction as well as diastolic dysfunction in patients of RA.
Material and Methods : Present study was conducted at Medicine Department of DMCH, Laheriasarai, Bihar. All patients (100 patients; 69 women and 31 men) diagnosed of RA based on ACR/ EULAR revised criteria, within the age group 18 – 65 yrs were selected for the study irrespective of duration or severity of the disease.
Results : The mean age of the participants was 43.01yrs. The duration of RA in participants ranged from 18yr to 64 yrs. They were sub classified into groups based on duration and the frequencies are demonstrated. It was observed that there is a significant correlation between the duration of the disease and presence of LV dysfunction.[Chi square value 14.23 compared to 3.84 with a p value of <0.001]
Conclusion : LV Dysfunction (systolic as well as diastolic) is more prevalent in RA patients than in general population and it has a high correlation with the duration and severity of the disease.

KEYWORDS

RA : Rheumatoid Arthritis; LV : Left Ventricular; LVDD : Left ventricular diastolic dysfunction; LVEF : Left ventricular ejection fraction.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology affecting 1-3 % of population with a female:male ratio more than 2:1, primarily involving synovial joints. The arthritis is marked by symmetrical peripheral polyarthritis including small joints, and usually leads, if uncontrolled, to destruction of joints due to erosion of cartilage and bone causing joint deformities. The disease usually progresses from the periphery to more proximal joints and results in significant locomotor disability within 10 to 20 years in patients who do not fully respond to treatment.

Although rheumatoid arthritis (RA) develops its central pathology within the synovium of diarthrodial joints, being a systemic disease, RA also results in a variety of extraarticular manifestations, particularly in patients with severe joint disease. Despite the differences in form and function, it is becoming clearer that the same cytokines that drive synovial pathology are also responsible for generating pathology in extraarticular tissues. Involvement of the musculoskeletal system other than joints and of organs not considered part of the musculoskeletal system occurs in about 40 percent of patients with RA over a lifetime of disease[1]. Extra articular involvement in RA is a marker of disease severity and is associated with increased overall morbidity and premature mortality. Successful management of systemic manifestations of RA is predicated upon control of the underlying joint disease and often includes glucocorticoid, DMARD and immunosuppressive treatments.

Rheumatoid arthritis is associated with increase in mortality due to acceleration of coronary and cerebrovascular atherosclerosis[2]. Overall, RA patients have shorter life spans compared to the general population. The mortality rates in patients with RA are 1.5– 1.6 fold higher than in the general population. The attributed causes of death appear overall similar to the general population, with cardiovascular disease being the most common attributed cause of death, followed by infection, pulmonary and renal disease[3].This fact was established by a Swedish study that found that, there was a significant increase in mortality among patients with RA compared with the general population and the most common cause of death in RA patients was cardiovascular events[4].

AIMS AND OBJECTIVES

AIMS

To evaluate left ventricular systolic dysfunction as well as diastolic dysfunction in patients of RA.

OBJECTIVES

1. To find the prevalence of LV dysfunction (systolic and diastolic) in patients of RA.
2. To assess relation between LV dysfunction with duration and severity of disease in patients with RA.

MATERIALS AND METHODS

Study Design

The present study was undertaken in the Department of Internal Medicine, DARBHANGA MEDICAL COLLEGE & HOSPITAL. This was a cross sectional study done on consecutive patients of rheumatoid arthritis who attended Medicine OPD and/or admitted at DARBHANGA MEDICAL COLLEGE AND HOSPITAL over a period of two year on a total of 100 patients.

Participants

All patients diagnosed of RA based on ACR/ EULAR revised criteria, within the age group 18 – 65 yrs were selected for the study irrespective of duration or severity of the disease. The participants with the

following conditions were excluded:

1. Pre-existing cardiac conditions especially CAD.
2. Diabetes Mellitus
3. Hypertension
4. Known endocrine disorders like hypothyroidism, Cushing's syndrome.
5. Blood Hb < 10 g/dl.
6. Patients with hepatic or renal dysfunction.

Participants were broadly assigned to three groups based on disease duration as:
Group A: duration < 5yrs,
Group B: duration 5-10 yrs
Group C: duration > 10 yrs

Definitions

- Rheumatoid Arthritis: a participant will be diagnosed to have RA if

he/she fulfils>= 6 Score in 2010 revised criteria by ACR and EULAR of 1987 ACR recommendations

- LV dysfunction: Defined as presence of either LV systolic dysfunction (LVSD) or LV diastolic dysfunction (LVDD) or both as confirmed by 2D ECHO and Colour Doppler studies including TDI
- LVSD: Any participant with left ventricular ejection fraction (LVEF) <55% assessed by 2D ECHO using M-mode Quinone's method.
- LVDD: Defined based on colour doppler measurement of E/A ratio, deceleration time (DT), e/e', IVRT with further grading as depicted in fig.1 below.

Interventions

A detailed history was taken from the patients regarding the duration and severity of RA, presence of any co-morbidity and symptoms of heart failure if any.

DAS – 28 score was calculated for each patient based on the number of swollen/ tender joint count, ESR and subjective assessment of disability. A clinical examination was done to look for any signs of heart failure in the form of pedal oedema, elevated JVP, pulmonary basal crackles or LV S3/S4etc as mentioned already.

Baseline investigations were done for all patients which included haemoglobin (Hb), acute phase reactants (ESR and CRP), liver and renal function tests (LFT / RFT). Any patient with Hb< 10g/dl, deranged LFT/ RFT was excluded from the study. A chest radiograph and electrocardiogram were obtained and examined for evidence of heart failure.

Thereafter all patients underwent a 2D Echocardiography done by a single cardiologist who was be blinded to the disease status. This was done using a Phillips iE 33 xMatrix Echocardiography system. A detailed evaluation of cardiac structure and function was done and entered in the proforma for each patient (Appendix B).

The LV systolic function was assessed using the M-mode Quinone's method by assessing the LV End Diastolic Diameter (LVEDD) and LV End Systolic Diameter (LVESD). The stroke volume (SV) is the difference between LVEDV and LVESV, and LV ejection fraction (LVEF) was calculated as $(LVEDD)^2 – (LVESD)^2 / (LVEDD)^2$, expressed as percentage. Further, LVEF was sub classified as shown in Table-1.

Table 1 – Grading of LVEF (Ref : Braunwald's Heart Disease)

LVEF	Interpretation	Grade
> 55%	Normal	0
45 – 55%	Mild	1
30 – 45%	Moderate	2
< 35 %	Severe	3

LV diastolic function was assessed using Doppler echocardiography and TDI by obtaining transmitral flow from the apical four-chamber/two chamber views. The sample volume was positioned at the tip of the leafletsof the mitral valve to record transmitral flow. The following variables were examined as parameters of left ventricular filling: peak of early diastolic (E) and late(or atrial) diastolic (A) flow velocity, E/A ratio,and deceleration time (DT), e/e' and IVRT. LV diastolic dysfunction was further graded as illustrated below in Table-2.

Table 2 - Grading of LVDD

Grade	LVDD	Interpretation
0	normal	normal diastolic function
1	mild	impaired relaxation
2	moderate	pseudonormal
3	severe	reversible restrictive
4	severe	fixed restrictive

Statistical Analysis

Descriptive statistics were used to summarise the demographics and echocardiographic features of subjects. Quantitative and qualitative demographic characteristics were summarised and data were tabulated. Results are presented in tabulated and graphical format. Data was expressed as mean standard deviation (SD), median (range 25th percentile to 75th percentile) and percentage.

For all the measurable data, two group means were compared using Chi-square test or Student's t-tests. For all the measurable data, more than two groups' means were compared using Analysis of Variance followed by multiple comparisons and post-hoc tests. The degrees of association between various measurable data were calculated using Pearson's coefficient of correlation. For all the categorical/classified data, the association of one category with the other category, we applied Chi-square test/Fisher's exact test whichever was applicable. A p-value of<0.05 was used to indicate differences between groups that were statistically significant.

RESULTS AND ANALYSIS

Baseline demographics and clinical characteristics

A total of 100 RA patients were enrolled during this study period. Women outnumbered men in the study population, with 69 women and 31 men. The mean age of the participants was 43.01yrs. The duration of RA in participants ranged from 18yr to 64 yrs. They were sub classified into groups based on duration and the frequencies are demonstrated below in fig.3. It was observed that there is a significant correlation between the duration of the disease and presence of LV dysfunction.[Chi square value 14.23 compared to 3.84 with a p value of <0.001].

DAS -28 scores of the participants ranged from 3.0 – 7.1.

Table : Duration of RA & LV dysfunction cases

RA duration distribution (years)	LV dysfunction cases
0-5	10
6-10	18
11-15	23

Table : DAS-28 score distribution & LV dysfunction relation

DAS-28 Score istribution	LV Dysfunction Cases	Normal LV Function Cases
0.49 – 3.1	3	11
3.2 – 5.1	21	20
5.2 – 9.07	27	18

There was also found to be a positive association between DAS- 28 score and the presence of LV dysfunction, when analysed using the Student's t-test (p <0.0001). Presence of LV dysfunction was found to be higher in patients with a higher DAS -28 score.

Symptoms of heart failure (dyspnoea, fatigue, edema and/or abdominal distension) were present in 19% of participants, in which the predominant symptom was dyspnoea. However clinical signs of HF could be found only in 12% of participants.

Echocardiographic findings

2D echocardiography derived results based on M-mode Quinone's method showed presence of LV systolic dysfunction in 15 participants, of which 04 had grade-1 LVSD (LVEF 45- 54%) and 03 had grade-2 (LVEF 30- 44%) LVSD and 08 had grade-3 LVSD (LVEF < 30%). The lowest LVEF recorded was 20.0%. In this study, in comparison with the standard data of LV Systolic Dysfunction in general population (6%) [38], the Chi Square Test showed a value of 14.3617 to 3.841 with a p value<0.001which is significant.

In terms of diastolic function measurements based on 2D echocardiography, colour doppler studies and TDI - LV diastolic dysfunction was present in 46 participants, of which 19 had grade-1 LVDD, 17 had grade-2 LVDD, 04 had grade- 3 LVDD and 06 had grade-4 LVDD. In this study, in comparison with the standard data of LV Diastolic Dysfunction in general population (27.3%), the Chi Square Test showed a value of 19.553 to 3.841 with a p value<0.001 which is significant.

Both figures combined, LV dysfunction (LVSD + LVDD) was present in 51 participants (51 %) of which 10 participants had both LVSD and LVDD.

Among other findings, mitral regurgitation (MR) was found in 08 patients, concentric LVH was present in 08, mild pericardial effusion detected in 03 and one patient had mild global hypokinesia of LV.

Disease Associations

The relationship between age of participant and the presence of LV dysfunction was analysed using Student's t- test. It was found that age had no significant relation with the presence of LV dysfunction (p =

0.186). In this study females had higher prevalence of occurrence of the disease than males. Also females showed relatively higher prevalence of LV dysfunction compared to males (68.62% and 31.37% respectively)as shown in fig.10.but when statistically analysed the incidence of LV dysfunction is almost the same (50.71% and 51.62%) irrespective of sex.

It was also observed that patients who have LV dysfunction found by screening are mostly asymptomatic than symptomatic and clinical signs of HF are present in only a smaller percentage of patients.

Table : Symptomatic & Asymptomatic patients with LV ysfunction in RA

RA cases with LV dysfunction	Symptomatic cases	Asymptomatic cases
51	19 (37.25%)	32 (62.74%)

Table : Patients with clinical signs of HF with LV dysfunction in RA

RA cases with LV dysfunction	HF signs present	HF signs absent
51	12 (23.52%)	39 (76.47%)

DISCUSSION

The results of the study shows an increased prevalence of LV dysfunction in patients of RA, compared to that of general population. 51% of participants showed presence of LV dysfunction [Vasan RS, Benjamin eat al 1999]. Furthermore, 15% had LV systolic dysfunction and 46% had LV diastolic dysfunction. 10% of above showed presence of both LVSD and LVDD.

The overall prevalence of LVSD in general population is 6% [Margaret M, Steven J et al JAMA 2003] and the prevalence of LVDD has been found to be as high as 27.3% [Kuznetsova T, Herbots L, Richard T et al 2009]. On comparison, there is clearly an increased prevalence of LV dysfunction in patients of RA. This difference seems significant in case of LVSD; however it is more significant for LVDD.

Many early studies have reported an increased incidence of LVSD in RA patients. Bhatia et al performed echocardiography in 226 RA patients and compared findings with local population estimates [Bhatia GB, Patel JV et al Cardiol 2006]. While systolic dysfunction (LVEF <50%) was more prevalent in RA patients (10.2% versus 5.3%), the patients were older than the population group and traditional cardiovascular risk factors had not been excluded, which would have contributed to the observed phenomenon. Depressed LV ejection fraction reported in a group of 100 RA patients compared with 100 matched controls [Wislowska M, Sypula S, Kowalik I, ClinRheumatol 1998]. While they excluded patients with hypertension, myocardial infarction, rheumatic fever, or a history of diabetes, their RA population had significantly more valvular heart disease than the controls (39% versus19%), possibly confounding the results.

In very recent studies, it has been discussed and shown that patients with rheumatoid arthritis (RA) have a high risk for cardiovascular disease due to a chronic inflammatory state, accelerated atherosclerosis, and changes in left ventricular (LV) geometry. These conditions predispose patients to LV systolic dysfunction (LVSD).It has been shown in a study that almost half of asymptomatic RA patients without history of cardiac disease have subclinical LVSD easily detectable with echocardiography and TDI --- RA is closely related to LVSD [Cioffi G, Viapiana Oetc, E Pub 2015].

In a study conducted by Rebecca et al [Arthritis Rheum. 2009] was found that LV mass is increased in RA patients independent of known risk factors. A study of strain analysis of LV function, found that patients with high disease activity and increased high anti-CCP titres had an increased LV dysfunction compared to patients with fewer symptoms and less disease activity in the very early phase of RA disease [Brian B, Lone K et al, Cardiovascular Dis 2014]. Studies By Gloria Arminio Berlinski, MS has shown that Echocardiographic results demonstrated, that, compared with matched control patients, those with RA had lower stress-corrected mid-wall shortening, as well as smaller LV diameters and volumes, increased relative wall thickness and mass, and greater concentric remodelling and hypertrophy. In particular, significantly more RA patients showed abnormal stress-corrected mid-wall shortening than did matched control patients (56% versus 15%; P<.001). Notably, the prevalence of impaired LV ejection fraction (defined as low if <50%) was comparable in study patients (3%) and control patients (1%) signifying increased incidence of LVSD in RA patients than general population. Multiple logistic regression analysis demonstrated that RA was associated with LVSD.

The association of RA with LVDD has also been conflicting, as found in earlier studies. In a study conducted by Kimberly P Liang et al [Ann Rheum Dis. 2010 Sep]comparing RA patients with general population, diastolic dysfunction was more common in subjects with RA at 31% compared with 26% (age and sex adjusted) in non-RA subjects. They also found that RA duration and interleukin 6 (IL-6) level were independently associated with diastolic dysfunction in RA even after adjustment for cardiovascular risk factors.

The present study shows that there is indeed a significant increase in prevalence of LVSD and also LVDD in patients of RA (15% and 46%) compared to general population (6% and 27.3%) {Chi Square Test 14.3617 / 3.841} and {19.55/ 3.814} showing a p value of <0.0001 and <0.0001 for each respectively.

CONCLUSION

LV Dysfunction (systolic as well as diastolic) is more prevalent in RA patients than in general population and it has a high correlation with the duration and severity of the disease.

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