A STUDY ON PREVALENCE OF DIASTOLIC DYSFUNCTION IN RHEUMATOID ARTHRITIS PATIENTS

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CERTIFICATE

This is to certify that this dissertation titled "**A STUDY ON PREVALENCE OF DIASTOLIC DYSFUNCTION IN RHEUMATOID ARTHRITIS PATIENTS"** submitted by **DR RAMYA. J** to the faculty of General Medicine, **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree **Branch I General Medicine**, is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

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This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the rules and regulations for the award of MD degree **(Branch I) General Medicine.**

Place: Madurai

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CONTENTS

ABSTRACT

Aims : The aim of this study was to evaluate the prevalence of diastolic dysfunction in rheumatoid arthritis patients and to compare them with age and sex matched controls. The correlation between diastolic dysfunction and disease activity was looked for.

Methods : The study was a cross sectional study involving 40 patients (8 maleand 32 female) with RA without clinically evident heart disease and 20 healthy subjects (16 female and 4 male) who served as a control group. Both groups were matched for age and sex. Echocardiographic and Doppler studies were conducted in all patients with RA and control subjects.

Results : Our study shows that patients with RA have a higher prevalence of diastolic dysfunction (40%) than non-RA subjects (10%) . The ejection fraction was preserved in all patients. The result in this study showed E/A ratio in RA patients was 1.135 (0.822–1.448) and in the control group was 1.305 (1.122–1.487). Dt in RA patients was longer compared to the control population (180 ms ± 27..77*vs*. 160.5 ms ± 11.95) with a significant p value.). The E/E′ index of RA patients was 8.447 ± 2.32 which was higher compared to the study population 7.946+/- 0.43. The LA volume indexed to body surface area was significantly higher in patients of RA compared to study group. It was 23.03+/- 7.53 in study group as compared to 18.18+/- 2.44 with a significant p value of 0.007. This study showed significant correlations between duration of disease, disease severity and echocardiographic measurements.There were no statistically significant differences between diastolic dysfunction and normal diastolic function groups in term of age of the patient, duration of disease, DAS 28, rheumatoid factor.

Conclusion: Prevalence of diastolic dysfunction in the rheumatoid arthritis group (40%) was higher compared to controls (10%). LV diastolic function had significant correlation with RA disease severity and duration of disease.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown aetiology that involves not only the joints but also other extra-articular organs. The prevalence of RA is ~0.8% of the population (range 0.3–2.1%); women are affected approximately three times more often than men (1). In India, the prevalence of rheumatoid arthritis (0.75%) is similar to that in the west (7,8).

Insights gained by a wealth of basic and clinical research over the past two decades have revolutionized the way we make the diagnosis and manage a case of RA. Serum antibodies to cyclic citrullinated peptides (anti-CCPs) are now recognized to be a valuable biomarker of diagnostic and prognostic significance. The clinical diagnosis of RA is largely based on signs and symptoms of a chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information. In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy(1).

The new criteria include a positive test for serum anti-cyclic citrullinated peptide antibodies as an item, which carries greater specificity for the diagnosis of RA than a positive test for rheumatoid factor. The newer classification criteria also do not take into account if the patient has rheumatoid nodules or radiographic joint damage because these findings occur rarely in early RA. It is important to emphasize that the new 2010 ACR-EULAR criteria are "classification criteria" as opposed to "diagnostic criteria" and serve to distinguish patients at the onset of disease with a high likelihood of evolving into a chronic disease with persistent synovitis and joint damage(1). In our study the patients have been diagnosed using the 1987 ACR classification criteria.

The 1987 Revised Criteria for the Classification of RA

1. a. Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA).

b. Patients with two or more clinical diagnoses are not excluded.

2. Criteria[a]

a. Morning stiffness: Stiffness in and around the joints lasting 1 h before maximal improvement.

b. Arthritis of three or more joint areas: At least three joint areas, observed by a physician simultaneously, have soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints.

c. Arthritis of hand joints: Arthritis of wrist, metacarpophalangeal joint, or proximal interphalangeal joint.

d. Symmetric arthritis: Simultaneous involvement of the same joint areas on both sides of the body.

e. Rheumatoid nodules: Subcutaneous nodules over bony prominences, extensor surfaces, or juxtaarticular regions observed by a physician.

f. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.

[a]Criteria a–d must be present for at least 6 weeks. Criteria b–e must be observed by a physician. ***Source:*** From Arnett et al.(28)

Classification Criteria for Rheumatoid Arthritis - 2010 ACR – EULAR		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, Thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	6weeks	1

Note: These criteria are aimed at classification of newly presenting patients who have at least 1 joint with definite clinical synovitis that is not better explained by another disease.

Abbreviations:

CCP - cyclic citrullinated peptides;

CRP - C-reactive protein;

ESR - erythrocyte sedimentation rate;

IP - interphalangeal joint;

MCP - metacarpophalangeal joint

MTP - metatarsophalangeal joint;

PIP - proximal interphalangeal joint; RF, rheumatoid factor;

ULN - upper limit of normal.

Source: Neogi et al: Arthritis Rheum 62:2569, 2010 (29).

REVIEW OF LITERATURE

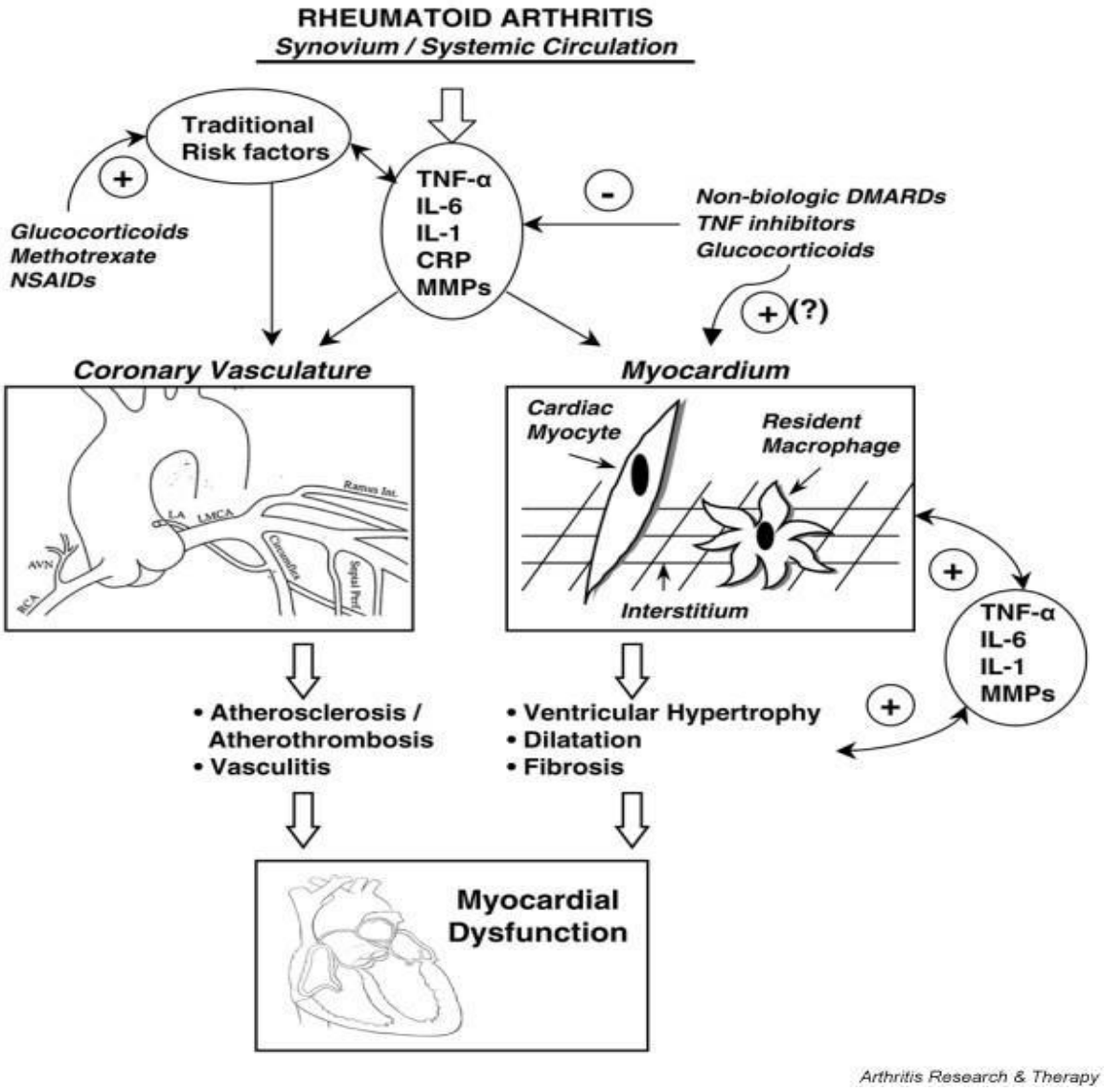
Long term survival of patients with rheumatoid arthritis (RA) is shorter compared with the general population or control subjects without RA (2). The most common cause of death in patients with RA is cardiovascular disease. Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population(4). The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease in this population as reported in many studies (3,4,5) . However, cardiac disease is often clinically silent and is rarely a severe life threatening complication in RA.

Rheumatoid arthritis is associated with increase in mortality due to acceleration of coronary and cerebrovascular atherosclerosis(11). 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 (12). This fact was supported by a recent study done in

Sweden 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 (12,13,14). RA patients are also more prone to atherosclerosis, myocardial infarction and stroke (14,15,16). Other possible complications that may arise include: pericarditis, myocarditis, atrioventricular block, valvular regurgitation, rheumatoid nodule, left ventricular failure, valvulitis and fibrosis (3).

The pathophysiology behind increased incidence of cardiovascular events in patients with RA is of considerable research interest and is vital for development of preventive strategies in future. Chronic inflammation is postulated to enhance the development of atherosclerosis in patients with RA. Pro-inflammatory cytokines, the levels of which are elevated in RA, have been found to play an important role in the development and progression of atherosclerosis. Now considered an inflammatory disease, atherosclerosis involves the production of pro-inflammatory cytokines by immune cells, such as monocytes, macrophages, and T-cells, at sites of atherosclerotic lesions, as well as by endothelial and smooth muscle cells. The chronic systemic inflammation seen in RA and systemic lupus

erythematosus (SLE) may further amplify atherosclerosis through endothelial dysfunction and oxidative stress. Pro-inflammatory cytokines (e.g. tumour necrosis factor α [TNF-α] and interleukin-1 [IL-1]), expressed by affected joints in RA, may act on other tissues and organs and promote atherosclerosis. (3)(30). The risk of heart failure can be partially explained by traditional cardiovascular risk factors and also involves disease-related factors such as high plasma interleukin (IL-6), C-reactive protein (CRP) and TNF-α levels, vasculitic processes and RA itself. (17)



Pathophysiologic mechanisms that may be involved in accelerated atherosclerosis and congestive cardiac failure associated with rheumatoid arthritis.

The cardiovascular manifestations of RA can take many forms. Clinically apparent heart disease attributable to rheumatoid process was previously thought to be rare. But of late because of advances in investigational facilities, various necropsy studies; several important studies have been performed which have highlighted the importance of cardiac involvement by RA. It is now reported that 70% of patients with nodular disease and 40% of patients with non-nodular RA have some cardiac involvement, including valve thickening or incompetence (3,10).

Of all the cardiovascular manifestations, two processes need our considerable attention here. First being accelerated atherosclerosis. Patients with prolonged RA have more atherosclerosis than patients of the same age with more recent disease onset (3,17). Persistent low grade inflammation associated with elevated levels of pro-inflammatory cytokines have been implicated for this increased risk (18). Second process which is of interest to our study will be elaborated below.

Cardiac failure is the result of either systolic or diastolic dysfunction or both. Left ventricular diastolic dysfunction is usually attributable to common structural abnormalities such as hypertrophy or interstitial fibrosis and impaired myocyte relaxation resulting from ischemia.

Compared with persons without RA, patients with RA have twice the risk of developing CHF (4). A large population based study conducted by Nicola et,al concluded that patients with RA have twice the risk of developing CHF compared with subjects without RA. This excess risk remained even after fully adjusting for CV risk factors and ischemic heart disease, and was higher in patients with RA who were RF positive than in those who were RF negative.

They observed that the increased risk of CHF among patients with RA is not attributable to an increased frequency or effect of either CV risk factors (i.e., hypertension, smoking, diabetes) or clinical ischemic heart disease, but rather, through independent RA or RA-disease associated factors (5). The risk of heart failure can only be partially explained by traditional cardiovascular risk factors and also involves disease-related factors such as high plasma interleukin (IL-6), C-reactive protein (CRP) and TNF-α levels, vasculitic processes and RA itself(17). In the large and well-studied population of rheumatoid patients at the Mayo Clinic, patients were followed until death, migration from Olmstead County, or 2001. The data showed that congestive heart failure was more important than ischemic heart disease as cause of death (5). Even in RA patients without

clinically evident cardiovascular disease, the left ventricular diastolic function and the right ventricular diastolic function are reduced(6,3). It has also been recently shown that RA subjects with HF have fewer typical signs and symptoms of HF and are more likely to have preserved ejection fraction (EF≥50%) compared to non-RA subjects with HF (18). Among RA subjects, the presentation of heart failure is more subtle, myocardial function is more likely preserved, while mortality from heart failure is significantly higher(19,20). Diastolic dysfunction in asymptomatic RA patients gradually progressing over years to overt cardiac failure has been presented as the most likely explanation of this form of presentation (18).

There are a number of studies that have reported the presence of diastolic dysfunction in patients with RA without clinically evident cardiac disease(21,22,23). Structural and functional alterations of the myocardium have been reported in numerous controlled, cross-sectional studies of RA subjects without known cardiovascular disease, suggesting impairment of diastolic function (4,5,15,17,20). These findings indicate that, compared to non-RA subjects, heart failure in RA may be more often related to diastolic dysfunction in comparison to the general population. Diastolic dysfunction is frequent and it can be asymptomatic for a long time. It can

be considered as the first step in the pathogenic pathway leading to heart failure. Other cardiovascular involvement such as myocardial fibrosis, granulomatous nodules, myocarditis, arteritis, amyloidosis and the use of cardiotoxic drugs, are also believed to be responsible for the development of diastolic impairment. At present, however, the direct effects of inflammatory cytokines (and rheumatoid arthritis therapies) on the myocardia of rheumatoid arthritis patients are incompletely understood.

Diastolic heart failure normally occurs before patients develop systolic heart failure. It is important to recognize diastolic heart failure (dysfunction) in any patient, particularly in RA, in order to retard progression of heart failure (20). The knowledge of diastolic dysfunction is beneficial in improving survival rates in RA patients.

A recently concluded study by Stephania Magda et al – CARRE study concluded that cardiovascular affection in RA is much higher compared to normals and is similar to that of diabetics(44). EULAR evidence based recommendations for management of rheumatoid arthritis suggest the following recommendations (45,46).

Recommendations :

Level of evidence Strength of recommendation

1. RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden 2b–3 B
2. Adequate control of disease activity is necessary to lower the CV risk 2b–3 B
3. CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed3–4 C
4. Risk score models should be adapted for patients with RA by introducing a. 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: 3–4 C

   – Disease duration of more than 10 years

   – RF or anti-CCP positivity

   – Presence of certain extra-articular manifestations

5. TC/HDL cholesterol ratio should be used when the SCORE model is used 3 C
6. Intervention should be carried out according to national guidelines 3 C
7. Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options 2a–3 C-D
8. The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors2a–3 C
9. Corticosteroids: use the lowest dose possible 3 C
10. Recommend smoking cessation 3 C

[ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AT-II, angiotensin II; coxibs, cyclo-oxygenase-2inhibitors; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SCORE, SystematicCoronary Risk Evaluation; TC, total cholesterol].

Doppler echocardiography is a sensitive and non-invasive method of detecting cardiac abnormalities and systolic and/or diastolic function (6). About 50% of patients with heart failure have preserved LVEF. Assessment of diastolic function requires an understanding of diastology and various means to evaluate diastolic function. Currently, echocardiography is the best noninvasive way to evaluate diastolic function and to estimate filling pressures. M-mode, two-dimensional, and Doppler (blood flow, tissue, and color) echocardiography are all helpful in evaluating diastolic function. Recently, the ASE and the European Association of Echocardiography (EAE) published a guideline for assessment of diastolic function by echocardiography which has standardised this previously ambiguous method of investigating diastolic dysfunction (24).

The grading of the diastolic filling pattern (or diastolic dysfunction) is based on several parameters (see figure below). In most (if not all) cardiac diseases, the initial diastolic abnormality is impaired relaxation. With further progression of disease and a mild to moderate increase in LA pressure, the mitral inflow velocity pattern appears similar to a normal filling pattern (pseudonormalized). With further decrease in LV

compliance and increase in LA pressure, diastolic filling becomes restrictive. Most patients with restrictive filling are symptomatic and have a poor prognosis unless the restrictive filling can be reversed by treatment. However, restrictive filling may be irreversible and represent the end stage of diastolic heart failure. Therefore, diastolic dysfunction can be graded according to the diastolic filling pattern (26). The grading scheme is mild or grade I (impaired relaxation pattern), moderate or grade II (PNF), and severe (restrictive filling) or grade III (figure below). This scheme was an important predictor of all-cause mortality in a large epidemiologic study (25).

Grade 1 (mild dysfunction): impaired relaxation with normal filling pressure.

Grade 2 (moderate dysfunction): pseudonormalised mitral inflow pattern.

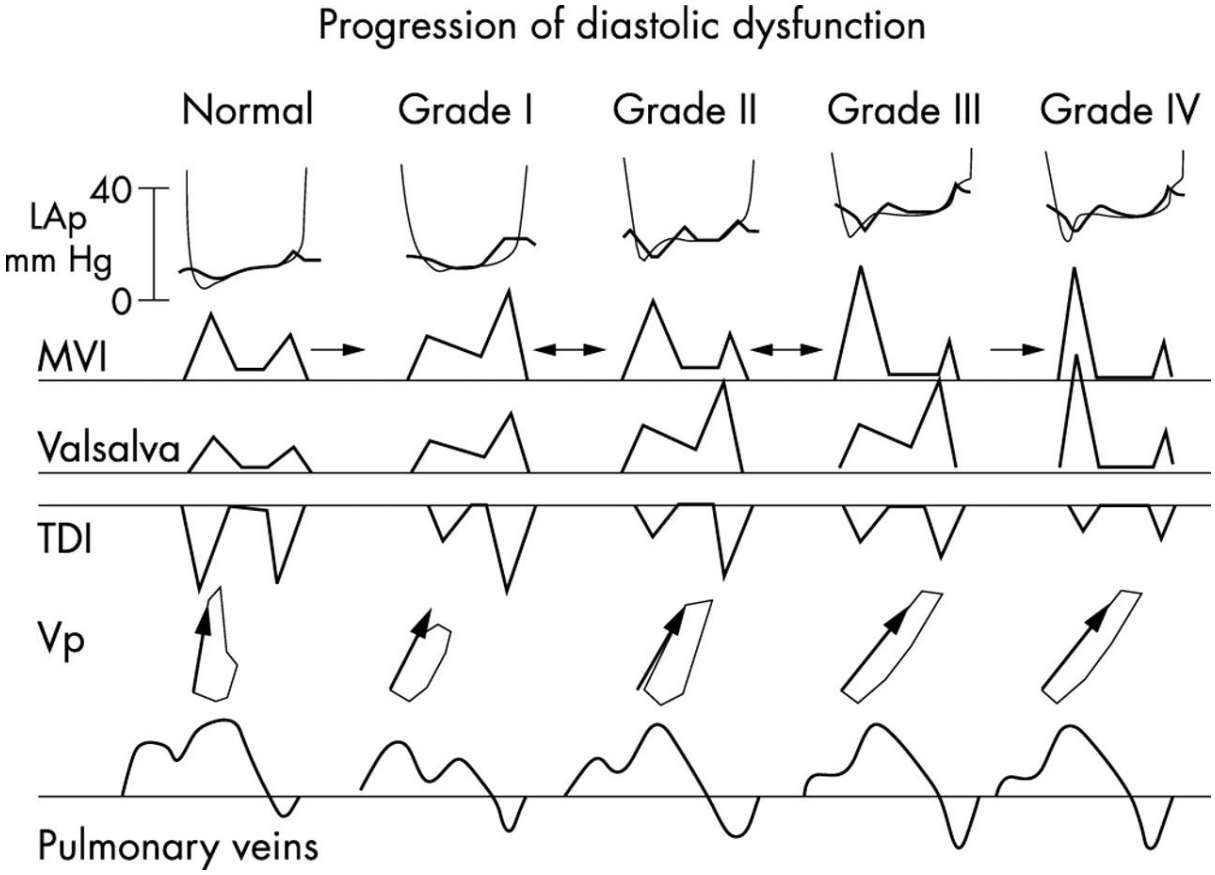
Grade 3 (severe reversible dysfunction): reversible restrictive (high filling pressure)

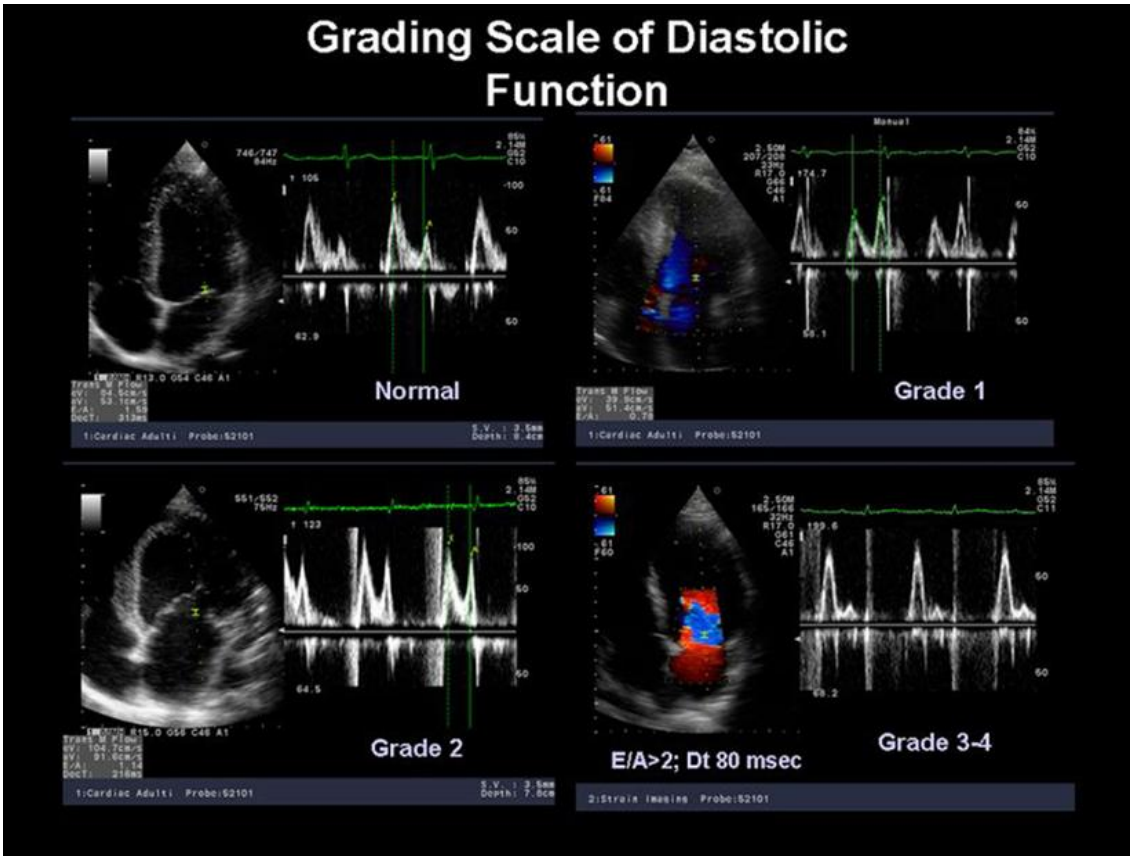
Grade 4 (severe irreversible dysfunction): irreversible restrictive (high filling pressure) (24).

In patients with mild diastolic dysfunction, the mitral E/A ratio is 0.8, DT is 200 ms, IVRT is 100 ms, predominant systolic flow is seen in pulmonary venous flow (S / D), annular e' is 8 cm/s, and the E/e' ratio is 8 (septal and lateral).

In patients with moderate diastolic dysfunction (grade II), the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by 50% during the Valsalva maneuver, the E/e' (average) ratio is 9 to 12, and e' is 8 cm/s.

With severe diastolic dysfunction (grade III), restrictive LV filling occurs with an E/A ratio 2, DT 160 ms, IVRT 60 ms, systolic filling fraction 40%, mitral A flow duration shorter than Ar duration, and average E/e= ratio 13 (or septal E/e' 15 and lateral E/e' 12). LV filling may revert to impaired relaxation with successful therapy in some patients (grade IIIa), whereas in others, LV filling remains restrictive (grade IIIb). Because the reversibility of restrictive filling usually cannot be assessed at one clinical setting, grade 4 dysfunction was not used in the ASE and EAE recommendation(26).


Progression of diastolic dysfunction
Normal
Grade I
Grade II
Grade III
Grade IV
LAp
mm Hg
40
0
MVI
Valsalva
TDI
Vp
Pulmonary veins


Grading Scale of Diastolic Function
Normal
Grade 1
Grade 2
E/A>2; Dt 80 msec
Grade 3-4

Assessment of left atrial volume is clinically important, because there is a significant relation (39) between LA remodeling and echocardiographic indices of diastolic function. Doppler velocities and time intervals reflect filling pressures at the time of measurement, whereas LA volume often reflects the cumulative effects of filling pressures overtime. LA volume index >/34 mL/m2 is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke(40). However, one must recognize that dilated left atria may be seen in patients with bradycardia and 4-chamber enlargement, anemia and other high-output states, atrial flutter or fibrillation, and significant mitral valve disease, in the absence of diastolic dysfunction. Likewise, it is often present in elite athletes in the absence of cardiovascular disease (26).

In normal young subjects, LV elastic recoil is vigorous because of normal myocardial relaxation; therefore, most filling is completed during early diastole. Thus, the E/A ratio is usually 1.5 or higher, DT is 160 to 240 milliseconds (septal), e′ is 10 cm/sec or higher, E/e′ is less than 8, and Vp is 50 cm/sec or higher. With normal myocardial relaxation, the longitudinal mitral annulus diastolic velocity pattern mirrors that of normal mitral inflow: early diastolic velocity (e′) is higher than late diastolic

velocity (a′). Lateral annulus velocity is always higher (normal, >15 cm/sec) than septal e′. Thus, e′ increases with exercise in healthy subjects so that E/e′ is similar at rest and with exercise (usually <8).[45] With aging, there is a gradual decrease in the rate of myocardial relaxation as well as in elastic recoil, resulting in slower decline of LV pressure, and filling becomes slower, producing a diastolic function pattern similar to grade 1 dysfunction. At roughly the age of 65 years, E velocity approaches A velocity, and in persons older than 70 years, the E/A ratio is usually less than 1.0. The reversal of e′/a′ occurs about 10 to 15 years earlier than that of E/A. Pulmonary venous flow velocities show similar changes with aging; diastolic forward flow velocity decreases as more filling of the left ventricle occurs at atrial contraction and systolic forward flow velocity becomes more prominent. Measurements of diastolic function in 1012 subjects without a history of cardiovascular disease or abnormal two-dimensional echocardiograms showed that all diastolic function parameters are associated with age(24).

AIM OF THE STUDY

To evaluate the prevalence of diastolic dysfunction in patients with rheumatoid arthritis and to compare them with age and sex matched controls.

To look for correlation between degree of diastolic dysfunction and

1. duration of the disease
2. severity of the disease

MATERIALS AND METHODS

Ours was a cross sectional study carried out for a period of 1 year. The setting was Department of Medicine, Govt Rajaji Hospital. Approval was obtained from the ethical committee headed by the Dean, Govt Rajaji Hospital. Informed written consent was obtained from all patients. Study population consisted of patients attending Rheumatology OP who were randomly selected. The data obtained was analysed using EPI Info 2002 statistical software.

The study was carried out on 40 patients attending the Rheumatology out patient department of Madurai Medical College with an established diagnosis of RA, as defined by the American College of Rheumatology 1987 criteria. 20 age and sex matched controls were selected from same population.

Patients were considered seropositive if the rheumatoid factor (Latex agglutination test) was positive (>8 IU/L) on atleast one occasion during the course of their disease.

All patients had been treated with nonsteroidal anti-inflammatory drugs (diclofenac, 100-150 mg/day) daily. Treatment with a DMARD was initiated when a diagnosis of RA was made. All the patients included in

our study were receiving one or more DMARD including chloroquine, sulfasalazine and methotrexate. Some of them were on low dose steroids (5-15mg/day) depending on severity of symptoms.

INCLUSION CRITERIA :

- Patients who satisfied the American College of Rheumatology 1987 criteria.
- Age group - 17 to 60 years irrespective of the sex
- Any duration of illness

EXCLUSION CRITERIA :

- Systemic hypertension
- Diabetes mellitus
- Ischemic heart disease
- Valvular heart disease
- Chronic systemic illness
- Chronic smoker
- Any other structural heart disease
- Obesity (BMI >30)
- Pregnacy
- ECG s/o left ventricular hypertrophy or any pathological q waves.

A questionnaire prepared noted the duration of RA, early morning joint stiffness, extra-articular complications, personal history including smoking, medications, domestic pets and occupation. The use of current and previous disease-modifying drugs, corticosteroid use, and. Analgesics was noted. Cigarette consumption was evaluated in pack years (1 pack yr = 20 cigarettes/day for 1 yr).

A detailed clinical examination consisting of recording of anthropometric parameters and blood pressure , the number of tender and swollen joints and systemic examination was performed. All patients had venous blood taken for full blood count, renal and liver function, lipid profile, serum uric acid, erythrocyte sedimentation ratio, C-reactive protein and immunological investigations included rheumatoid factor (latex agglutination test).

All patients underwent chest radiography, electrocardiogram (ECG), echocardiography.

The activity of the disease was assessed using DAS 28(Disease activity score)Disease activity score is a composite score using tender and swollen joints count , ESR and patients global assessment activity using a 100 mm visual analogue scale.

DAS28=0.56 √(no.of tender joints) + 0.28 √(no.of swollen joints) +0.70 log(ESR)+0.014(global assessment in mm).

Classification

Mild	<3.2
Moderate	3.2-5.1
Severe	>5.1 (Minimum score :0; Maximum score : 9)

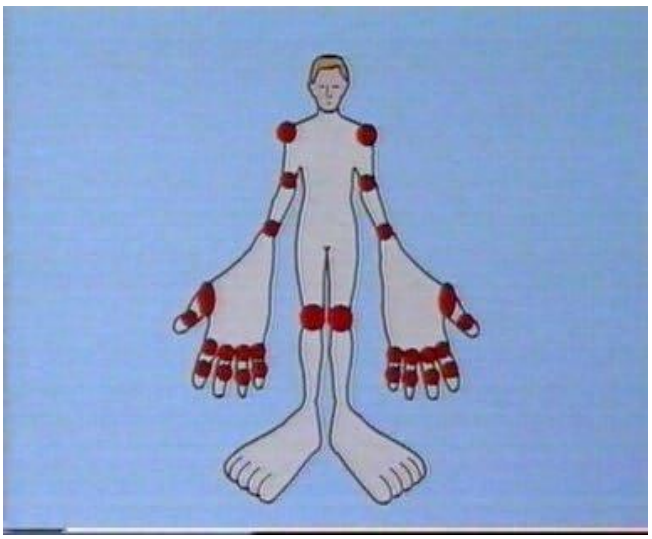
Parameters used in Disease activity score:

(1) Total 28 joint count for tenderness

(2) Total 28 joint for swelling

(3) ESR in mm in first hour

(4) Patient assessment of global health using a 100mm visual analogue scale ranging from 0(very good) to 100 (very poor)



ECHOCARDIOGRAPHY :

Two-dimensional and M mode echocardiography was performed using ALOKA echocardiogram. One senior cardiologist performed the echocardiography. The cardiologist was blinded to clinical details of the patients. The following variables were assessed using the 2 – dimensional echo - left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left atrial volume, left ventricular mass.

Fractional shortening and ejection fraction were calculated according to Simpson's formula. Special attention was paid to the structure of the mitral, aortic, tricuspid, and pulmonary valves (different grades of regurgitation and stenosis were assessed), and the pericardial space to detect pericardial effusion.

Doppler echocardiography was used to obtain transmitral flow from the apical four-chamber view to assess filling patterns. The following variables were examined as parameter of left ventricular filling:

Peak of early diastolic (E) and late diastolic (A) flow velocity, E/A ratio, deceleration time (Dt) of early filling velocity.

Colour M mode was used to look for mitral inflow propagation velocity.

Tissue Doppler imaging (TDI) was performed to look for the longitudinal motion of the mitral annulus which has been shown to correlate with the rate of myocardial relaxation. The velocity of the mitral annulus can be recorded by TDI

To assess the diagnostic validity of the results of the echocardiogram, a control group for echocardiogram readings was incorporated into the study. .

Echocardiography was undertaken with the same ALOKA echocardiogram by the same cardiologist who performed the echocardiography in the patients with RA.

STATISTICS

Data analysis was done using epidemiological information statistical software. Using the software the frequencies, mean , standard deviation and p values calculated chi square test and one way anova for quantitative variables. p value <0.05 is taken as significant. The correlation between various variables were performed using Pearson correlation technique and charted on scatter diagram.

RESULTS

Baseline demographics and clinical characteristics

The study was conducted from December 2010 to November 2011 recruiting subjects from the Rheumatology Outpatient Clinic of Government Rajaji Hospital, Madurai. A total of 40 RA patients and 20 control subjects were enrolled during this study period. Women outnumbered men in the study population, with 48 women and 12 men.

TABLE - 1

Age Distribution

Age in years	Cases	Controls
17 – 25	2	1
26 – 35	16	4
35 – 45	13	10
> 45	9	5
Total	40	30
Mean	39.0	41.0
SD	9.64	9.2
'p' value	0.445 Not significant	

In our study age of individuals varied between 20 and 60 years. The ages of study and control groups were matched. The mean age of study group was 39 and that of control group was 41 years.

AGE DISTRIBUTION

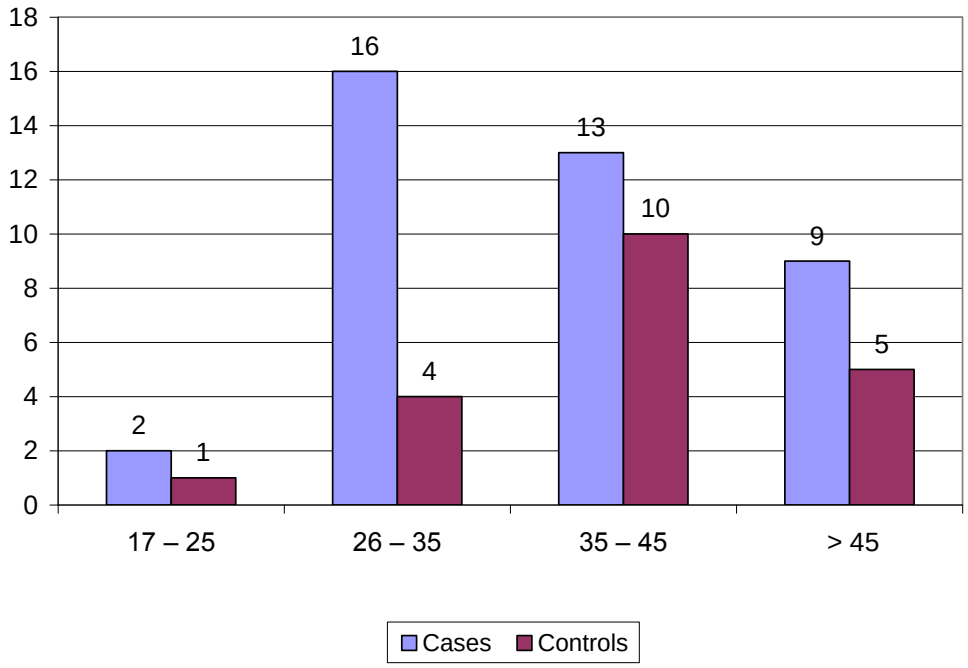


TABLE - 2

Sex Distribution

Sex	Cases	Controls
Male	8	4
Female	32	16
Total	40	20

Of the 40 individuals in the study group 32 were women and 8 were men in a ratio of 4:1. Similarly in the control group a ratio of 4:1 was maintained with 16 individuals being female and 4 being male.

SEX DISTRIBUTION

TABLE – 3

Baseline clinical characteristics

Parameters	Cases	Control	P value
Age	39	41	0.445
Sex:			
Female	32	16	
Male	8	4	
BMI	22.61	22.40	0.826
Systolic BP	120.0	120.5	0.854
Diastolic BP	80.0	81.0	0.571

The baseline clinical characteristics listed in table 3 , shows that the cases and the control population had similar age and sex distribution, similar BMI and blood pressure measurements. There was no statistically significant difference between the baseline characteristics of the two groups.

TABLE – 4

Echocardiographic Measurements in RA and Control groups

	Cases		Controls			
	Mean	SD	Mean	SD	P value	
E/A	1.135	0.313	1.305	0.182	0.029	Significant
E/E’	8.447	2.32	7.946	0.43	0.344	Not Significant
Dt	180.92	27.77	160.5	11.95	0.003	Significant
Vp	60.29	10.39	60.45	6.08	0.95	Not Significant
EF%	62.78	5.49	60.80	4.01	0.159	Not Significant
LAVI	23.03	7.53	18.18	2.44	0.007	Significant

[E – early diastolic filling; A- late diastolic filling; Dt – deceleration time of early diastolic mitral flow; Vp – flow propagation velocity; EF – ejection fraction; LAVI – left atrial volume index]

Two dimensional echocardiography M – mode and tissue doppler studies show that there is no statistically significant difference in ejection fraction and propagation velocity of the two groups. Statistical analysis of the filling velocities show that there is a statistically significant difference between E/A ratios of the two population. The comparison of mean E/e’ ratio between cases and control also show a statistically significant difference. However the deceleration time between the two population do not show any significant difference.

TABLE - 5

Diastolic dysfunction in RA and Control groups

Grade	Cases	control	P value
Normal	24	18	0.441
Grade 1	10	2	
Grade 2	6	0	0.124
Grade 3	0	0	
Prevalence	40%	10%	

Of the 40 cases evaluated by echocardiography 10 had grade 1 diastolic dysfunction and 6 had grade 2 diastolic dysfunction. Of the 20 control subjects 2 had grade 1 diastolic dysfunction and none had grade 2 dysfunction. Comparison between the two is statistically significant.

DIASTOLIC DYSFUNCTION

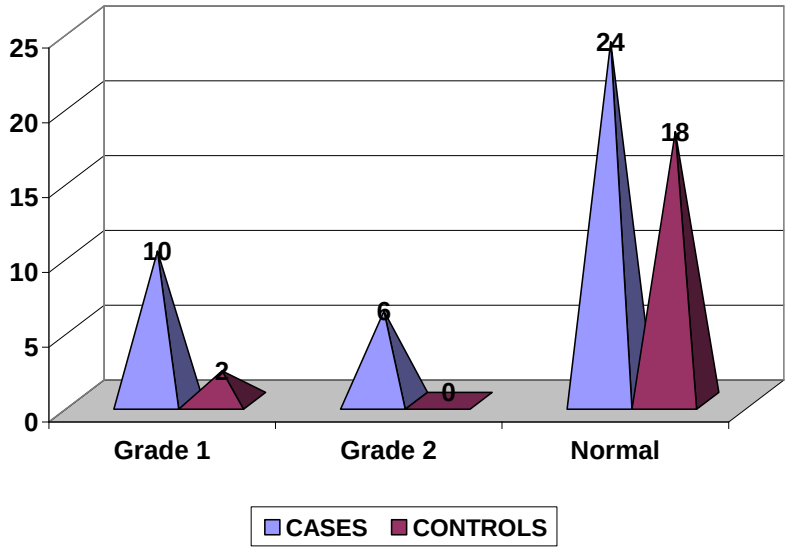


TABLE - 6

Diastolic Dysfunction and Rheumatoid factor.

Rheumatoid factor	Positive	Negative
Number	21	19
Prevalence of diastolic dysfunction	8	8

Among 40 cases studied 21 had RF positivity; 8 of these had diastolic dysfunction. Remaining 19 were RF negative, 8 of these had diastolic dysfunction. There is no stastistically significant difference between these two groups.

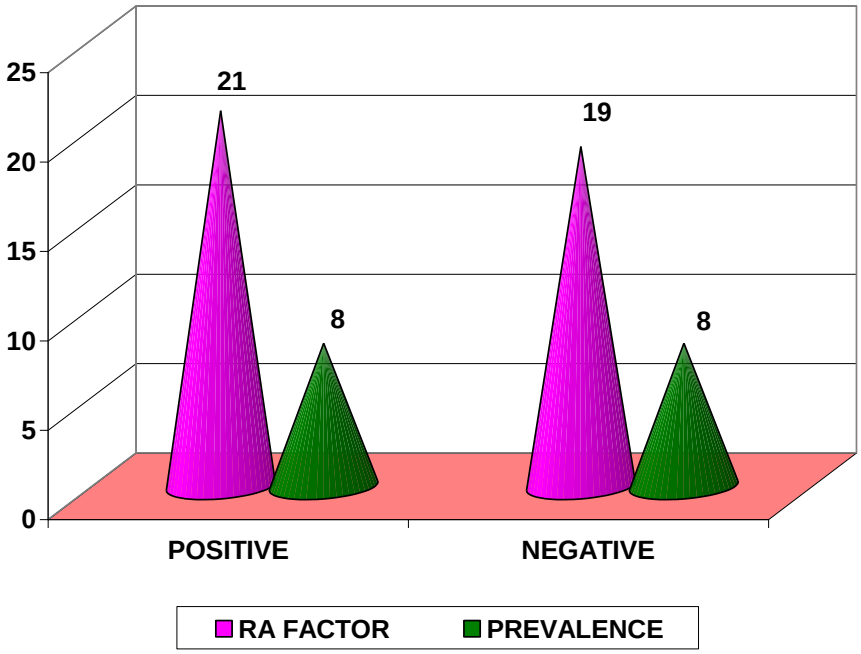

25
20
15
10
5
0
21
8
19
8
POSITIVE
NEGATIVE
RA FACTOR
PREVALENCE

TABLE - 7

Diastolic dysfunction and sex distribution

Dysfunction	No.of cases
Male	2
Female	14

Among the study population who had diastolic dysfunction 14 were females, 2 were males.

Correlation between diastolic parameters and baseline characteristics in RA patients.

TABLE – 8

Correlation of L A volume with disease characteristics

LAV Vs	LAV (Mean – 23.03 SD 7.53)		
	Mean	S.D.	P value
Age	39.0	9.64	< 0.001
Duration	4.34	4.23	< 0.001
DAS 28	4.21	1.31	< 0.001
ESR	53.6	24.53	< 0.001
BMI	22.61	3.79	< 0.001

Mean LA volume shows positive correlation with duration of disease, ESR and DAS28 score of the patients.

TABLE – 9

Correlation of E/A ratio with disease characteristics

E/A Vs	E/A (Mean – 1.135 SD 0.313)		
	Mean	S.D.	P value
Age	39.0	9.64	< 0.001
Duration	4.34	4.23	< 0.001
DAS 28	4.21	1.31	< 0.001
ESR	53.6	24.53	< 0.001
BMI	22.61	3.79	< 0.001

The E/A ratio shows positive correlation with the duration of the disease, ESR and DAS28 score of the study population.

Table – 10

Correlation of base line characteristics in RA patients with or without diastolic dysfunction

	Mean		P value
	With dysfunction	Without dysfunction	
Age	43.75	35.72	0.007
Duration	5.76	5.28	0.065
DAS 28	4.69	3.90	0.056

In case of age, between the two groups there is statistically difference. In case of both duration and disease active score there is statistically significant difference between the two groups

DISCUSSION

Introduction :

Cardiovascular disease has been a well-recognized complication of RA for decades(30). Several studies have been performed which show a higher prevelance of diastolic dysfunction in this population compared to control population. Studies also have been performed to indicate that this might precede congestive heart failure by several years which is an important cause for increased mortality among these population (15)(5)(18).

Demographics and clinical characteristics :

Ours was a cross sectional clinic based study carried out on 40 RA patients (8 men and 32 women, mean (standard deviation [SD]) age 39.0(9.64) years, range(21–50 years). Duration of the disease ranged from less than 1 year to 20 years. We had an age and sex matched control population of 20 individuals. Both cases and controls belonged to south India. These demographics are similar to a study conducted by Udayakumar et.al on same population (south Indian) which consisted of

45 RA(36 women and 9 men) and 45 control subjects, mean age of 34.8 and a disease duration ranging from 1 to 17 years.(31).

Echocardiographic measurements and diastolic dysfunction :

Our study shows that patients with RA have a higher prevalence of diastolic dysfunction (40%) than non-RA subjects (10%) . Diastolic dysfunction was more common in RA than in the non-RA subjects even after adjustment for or matching for CV risk factors. Doppler echocardiogram was the method used to evaluate diastolic function. It measured E, A, E/A ratio, DT and IVRT. These parameters were used to classify the diastolic dysfunction. Diastolic dysfunction in this study was classified according to Redfield(32). The prevalence was similar to Udayakumar *et al(31)* who noted a prevalence of 42.2%. Other studies like Kimberly p Liang et al and Abo Malek Abdul Miuzz et al have reported a prevalence of 31% and 47.2% respectively.(33)(34)

Many studies have compared individual doppler parameters between cases and control population. From these study parameters E and E/A ratios were found to be lower in patients with RA compared with the control group. The result in this study showed E/A ratio in RA patients

was 1.135 (0.822–1.448) and in the control group was 1.305 (1.122–1.487), which was concordant with the above literature. (22)(33)(34).

Deceleration of inflow of the E wave was measured by deceleration time (Dt), which shortened with decreasing LV compliance. A short Dt, a marker of increased LV chamber stiffness, has been shown to predict cardiovascular (CV) events. In contrast, a longer deceleration time, reflective of delayed LV relaxation, has also been shown to predict poor CV outcomes(35). Dt in RA patients was longer compared to the control population (180 ms ± 27..77*vs*. 160.5 ms ± 11.95) with a significant p value. Wislowska *et al(9).* reported Dt in RA was longer compared to the control group (240 ms ± 23 *vs*. 219 ms ± 48).

Tissue Doppler imaging (TDI) was the other method to evaluate diastolic function. TDI measures myocardial velocities during the cardiac cycle by determining the transmitral flow velocity to annular velocity ratio (E/E′ index)(36) TDI was considered more reliable for diagnosing diastolic dysfunction(37). In this study E/E′ index of RA patients was 8.447 ± 2.32 which was higher compared to the study population 7.946+/- 0.43. This parameter was noted to be shorter compared to Arslan *et al(21)* and Birdane *et al(38).*

There was no significant difference in propagation velocity in the study and control group 60.29+/-10.39 vs 60.45+/- 6.08.

LA volume indicates cumulative effects of filling pressures over time. LA volume index of 34 mL/m2 is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke.(40) (43). In our study LA volume indexed to body surface area was significantly higher in patients of RA compared to study group. It was 23.03+/- 7.53 in study group as compared to 18.18+/- 2.44 with a significant p value of 0.007.

Analysis in RA patients.

Further analysis was performed in RA patients to find significant values between diastolic dysfunction and normal diastolic function groups. We found no statistically significant differences in terms of age of patient, duration of RA and ESR. This finding was similar to the study done by Gonzalez-Gay *et al.*,(47) in which their subgroup analysis found there was no statistically significant difference in terms of disease duration between diastolic dysfunction and normal diastolic function groups. There was also no statistically significant difference in prevalence of diastolic dysfunction among rheumatoid factor (RF) positive and negative group.

Correlation between diastolic dysfunction and duration of the disease.

In this study, there was statistically significant correlation between duration of disease and alteration of diastolic function as expressed by E/A ratio. There was also significant correlation between duration and LA volume index. The study done by Di Franco *et al(22).* and Montecucco *et al(41)Arsalan et al(23).(*found that there were significant correlations between alteration of diastolic function expressed by E/A ratio and disease duration of RA. This means that as RA progresses, the prevalence of diastolic dysfunction increases as measured by E/A ratio.

Correlation between diastolic dysfunction and severity of disease

DAS-28 was used for objective assessment for RA disease severity. The level of ESR was also used to correlate with distolic dysfunction. In this study, there was statistically significant correlation between echocardiographic measurement values as expressed by E/A ratio and LA volume index in RA patients and values of DAS-28 and ESR. This implies that when the severity of the disease is higher the prevalance of diastolic dysfunction is also higher. A study done by Maradit-Kremers *et al.(42)* found that RA patients with new onset of heart failure, had a higher ESR

level at diagnosis up to 6 months after diagnosis. Kimberly p liang et al(33) have found correlation between interleukin-6 (as a marker of disease activity) and diastolic dysfunction in RA patients. Certain others such as the recently published Abdul Muizz et al have found no significant correlation.

CONCLUSION

In conclusion, the prevalence of diastolic dysfunction in RA patients attending at the Rheumatology Outpatient Clinic in Government Rajaji Hospital, was 40% and prevalence of diastolic dysfunction in the control group was 10%. This study showed significant correlations between duration of disease, disease severity and echocardiographic measurements.

Further analysis in RA patients noted that there were no statistically significant differences between diastolic dysfunction and normal diastolic function groups in term of duration of disease, blood pressure, ESR. There was also no statistically significant association in RA patients in term of presence of Rh factor, DAS-28 between diastolic dysfunction and normal diastolic function groups.

This study highlights the need for assessment of diastolic parameters in all patients with RA and periodic follow up of the same. Since diastolic dysfunction is considered a forerunner for future development of cardiac failure in these patients physicians and rheumatologists should be on alert and possibly delay this complication by timely intervention.

Prospective clinical and echocardiographic evaluation in RA cohorts are needed not only to dissect the importance of disease itself but also to learn about the effect of DMARDs and biologicals in retarding this process.

SUMMARY

The study “Prevalance of Diastolic Dysfunction in Rheumatoid Arthritis ” is a cross- sectional study conducted on patients visiting the outpatient Department of Rheumatology ,Government Rajaji Hospital, Madurai.

Forty patients with rheumatoid arthritis fulfilling the criteria of American rheumatologist association criteria (1987) were included in the study. Twenty age and sex matched control population were selected from same population. Inclusion and exclusion criteria were strictly followed in selecting case and control cohort. Selected patients underwent clinical, and laboratory evaluation to assess the severity of disease, activity of disease and to rule out any associated confounding lab parameters. DAS 28 score was calculated as an indicator of the disease severity. Both case and control cohort underwent echocardiography and diastolic parameters were assessed. Statistical analysis revealed that the patients with rheumatoid arthritis had a higher prevalence of diastolic dysfunction as compared to the control population and diastolic dysfunction correlated well with the duration of the disease as well as severity of the disease.

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A STUDY ON DIASTOLIC DYSFUNCTION IN RHEUMATOID ARTHRITIS

Name:

Age: Sex:

Address:

Ph :

CLINICAL FEATURES

Duration of illness

Disease activity : Active Not active DAS 28

Articular : EMS >1hr <1hr <1/2hr <1/4hr

Extra – articular :

Eye –SiccaScleritisEpiscleritis

Rheumatoid Nodules

Vasculitic Ulcer

ILD

CO-MORBITIES – SHT, DM, IHD, Obesity, Hyperlipidaemias'

Smoking/ Alcoholism/Tobacco chewing

TREATMENT DETAILS

NSAID's Steroids DMARD's

LABORATORY VALUES

RF positive negative

RF titre CRP ESR CBC

RFT LipidProfile S Uric acid LFT

IMAGING STUDIES

CXR CT ratio Lung fields

ECG Rhythm Conduction abn LAE LVHPul HTN/RVH e/o IHD

ECHO LVID AR HtWt BSA

LVIDs MR

EF TR Pul A pressure

LV mass LV mass index

E S' E/A

A E' E/E'

Dt A'

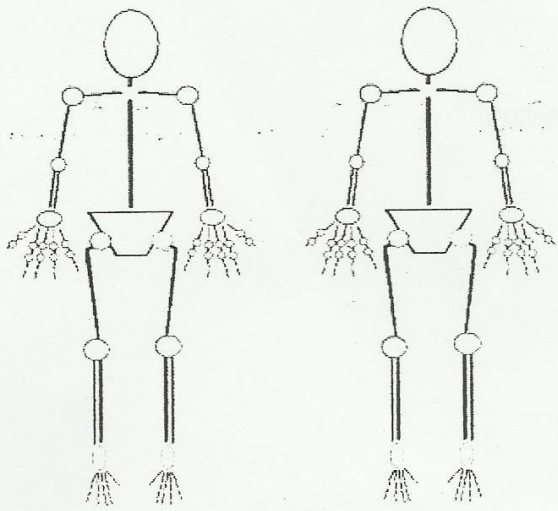
Vp

LA volume - A1 A2 L

LA volume index

~~LAvolume~~LA~~volume~~ ~~indexed to~~ BSA

~~Pulmonary~~ ~~artery~~ ~~pressure~~



TENDER SWOLLEN

MASTER CHART – CASES

S.No.	name	age	sex	habits	DM	SHT	IHD	BMI	SBP	DBP	T Chol	TGL	LDL
1	Panchu	35	F	none	nil	nil	nil	23.8	110	70	209	217	125
2	Kurshida	43	F	none	nil	nil	nil	21.5	120	80	190	170	130
3	Jothimani	40	F	none	nil	nil	nil	21.8	110	80	103	132	36
4	ponnusami	38	M	none	nil	nil	nil	29.6	110	70	146	150	102
5	valarmati	34	F	none	nil	nil	nil	15.8	100	70	160	190	90
6	Kripavati	41	F	none	nil	nil	nil	34.7	130	80	248	234	140
7	valarmati	48	F	none	nil	nil	nil	21.6	110	80	178	150	98
8	Muthaiah	33	M	none	nil	nil	nil	17.9	110	80	180	160	90
9	Kani	33	F	none	nil	nil	nil	23.6	120	70	198	165	98
10	Meena	28	F	none	nil	nil	nil	17.8	130	80	157	133	87
11	Durai	33	M	smoker	nil	nil	nil	20.8	120	80	178	144	80
12	Parvati	32	F	none	nil	nil	nil	24.5	110	80	165	134	78
13	Pandi	56	M	none	nil	nil	nil	21.9	130	80	186	165	89
14	Sheela	53	F	none	nil	nil	nil	26.8	110	90	202	189	110
15	Shanti	41	F	none	nil	nil	nil	24.4	110	80	164	150	88
16	Murugan	42	M	none	nil	nil	nil	21.5	120	80	172	144	78
17	Panchavarnam	45	F	none	nil	nil	nil	19	140	90	180	160	80
18	Subashini	41	F	none	nil	nil	nil	21.5	140	90	170	140	67
19	Periyatchi	55	F	none	nil	nil	nil	25.5	140	90	180	164	89
20	Jeyalaxmi	40	F	none	nil	nil	nil	26.5	140	90	168	140	80
21	Manimala	55	F	none	nil	nil	nil	22.2	130	80	178	150	76
22	Ramar	43	M	none	nil	nil	nil	18.4	120	80	198	148	128
23	Sumati	41	F	none	nil	nil	nil	31.2	130	80	214	190	156
24	Shyamala	53	F	none	nil	nil	nil	22.4	120	80	190	176	140
25	Maheswari	53	F	none	nil	nil	nil	24.5	110	80	149	186	71
26	Subbulaxmi	28	F	none	nil	nil	nil	25.8	110	80	118	124	53
27	Mumtaz	19	F	none	nil	nil	nil	21.9	110	70	124	145	65
28	Jayanti	28	F	none	nil	nil	nil	21.5	110	90	165	140	68
29	Shankar	53	M	none	nil	nil	nil	17.1	130	90	205	106	139
30	Nagajoti	28	F	none	nil	nil	nil	25.8	130	80	118	124	53
31	Parameswari	45	F	none	nil	nil	nil	22.5	120	80	178	160	78
32	Muniamm	29	F	none	nil	nil	nil	18.6	120	80	140	98	68
33	Mariamma	33	F	none	nil	nil	nil	20.8	110	70	168	134	87
34	Latha	48	F	none	nil	nil	nil	23.2	120	80	180	167	110
35	Hema	31	F	none	nil	nil	nil	24.6	110	70	178	198	96
36	jJeya	21	F	none	nil	nil	nil	19.2	110	70	156	167	78

37	Parasakti	33	F	none	nil	nil	nil	21.6	130	80	180	196	120
38	Mahalaxm	33	F	none	nil	nil	nil	22.4	130	90	172	144	78
39	Ravi	43	M	none	nil	nil	nil	18.4	120	70	149	186	71
40	Kamala	32	F	none	nil	nil	nil	21.9	120	90	201	179	100

S.No.	CRP	ESR	DMARDS	others	ECG	CXR	E/A	E/E'	Dt	Vp	E F%	LA V I	DYSFn	normal	
1	neg	60	yes	yes	N	N	1.38	10	161	60	71	33.98			
2	pos	80	yes	yes	N	N	1.22	5.38	164	58	71	17		plus	
3	neg	38	yes	yes	LAE	N	0.58	6.71	220	48	62	22.14			p
4	neg	40	yes	yes	N	N	1.77	13	193	53	57	14.69			
5	neg	45	yes	yes	N	N	1.433	14.87	187	73	73	19.04			
6	pos	70	yes	yes	LAE	N	1.142	10.52	150	70	59	33.96			
7	pos	75	yes	yes	N	N	0.63	8.59	245	85	67	20.98			p
8	neg	75	yes	yes	N	N	1.09	8	171	67	59	32.58		plus	
9	neg	100	yes	yes	N	N	0.84	16.16	237	53.3	66	16.48			p
10	neg	50	yes	yes	N	N	1.43	5	159	52.5	61	19.79		plus	
11	neg	26	yes	yes	N	N	1.435	8.09	145	64.4	64	32.29		plus	
12	pos	55	yes	yes	N	N	1.44	6	182	56	64	27.4		plus	
13	neg	40	yes	yes	N	N	0.689	7.28	221	48	60	18.79			p
14	neg	35	no	yes	N	N	0.78	8	190	52	56	29.44			p
15	neg	40	yes	yes	N	N	1.23	7.3	164	63	71	18.2		plus	
16	neg	85	yes	yes	N	N	1	7.62	174	84	68	16.82		plus	
17	neg	40	no	yes	N	N	0.55	6.28	214	56	52	43.8			p
18	neg	50	yes	yes	N	N	1.29	7.33	180	50	61	15.03		plus	
19	neg	42	yes	yes	N	N	0.758	10.45	158	41	60	29.8			
20	neg	30	yes	yes	N	N	1.3	11.25	161	60	55	17.96		plus	
21	neg	48	yes	yes	N	N	0.7	9.8	249	47	68	27			p

22	neg	60	yes	yes	N	N	1.166	5.6	200	56	65	19.45		plus	
23	neg	60	yes	yes	N	N	1.02	8.875	220	60	74	12.15		plus	
24	neg	95	yes	yes	n	n	1.01	7.77	196	60	64	11.73		plus	
25	neg	110	no	no	N	N	0.795	11.14	193	60	69	18.39			p
26	neg	10	yes	yes	N	N	1.5	7.41	148	82	62	14.75		plus	
27	neg	60	no	yes	N	N	1.5	7.41	160	70	62	19.88		plus	
28	neg	40	yes	yes	N	N	1.11	8	180	68	60	23.35		plus	
29	neg	60	yes	yes	N	N	1.24	6.615	187	60	60	36.45		plus	
30	neg	10	yes	yes	N	N	1.5	7.41	148	82	62	14.75		plus	
31	neg	30	no	yes	N	N	1.2	8.4	168	54	66	18.3		plus	
32	neg	50	yes	yes	N	N	1.3	8.9	170	58	60	22.4		plus	
33	neg	60	no	yes	N	N	0.7	7.41	145	50	60	26.7			p
34	pos	120	yes	yes	N	N	0.68	7.62	140	54	58	28.7			p
35	neg	25	yes	yes	N	N	1.29	8.33	180	58	60	27.8		plus	
36	neg	40	no	yes	N	N	1.44	8.875	190	64.4	56	29.44		plus	
37	neg	50	yes	yes	N	N	1.3	7.85	161	65	52	17.96		plus	
38	neg	40	yes	no	N	N	1.29	7.33	180	50	61	15.03		plus	
39	neg	60	yes	yes	N	N	1.44	8	182	56	64	27.4		plus	
40	neg	40	yes	yes	N	N	1.23	7.3	164	63	71	29.44		plus	

MASTER CHART – CONTROLS

S.No.	name	age	sex	SBP	DBP	BMI	E/A	E/E'	Dt	Vp	EF	Lavol I	N	
1	lakshmi	32	F	120	80	22.6	1.45	6.18	167	67	68	18.78	n	
2	panimalar	28	F	110	70	19.2	1.18	8	160	68	60	16.4	n	
3	ponraj	45	M	130	80	23.4	1.23	6.6	170	66	66	21.9	n	
4	vasanti	49	F	120	80	22.4	1.48	9	186	67	64	18.9	n	
5	kripa	39	F	110	80	20.7	1.63	7.9	156	56	64	17.8	n	

6	salma	41	F	130	90	28.8	1.18	6.36	140	54	58	19.7	n	
7	muthu	22	F	120	80	18.7	1.26	7	177	67	58	13.78	n	
8	kanimozhi	53	F	130	90	22.7	1.41	7	146	60	58	18.78	n	
9	pandiselvi	33	F	120	80	18.8	1.21	8.67	160	72	62	14.8	n	
10	shajira	54	F	110	80	23.7	0.84	8	150	54	58	22.8		
11	vellamma	41	F	120	80	21.6	1.32	8.3	169	56	54	16.9	n	
12	muthiah	42	M	120	80	23.4	1.45	7.22	154	60	62	20.05	n	
13	manimegal	41	F	140	90	21.2	1.38	8.2	144	58	67	17.7	n	
14	parasakti	55	F	130	80	21.8	0.78	7.7	154	52	60	19.8		
15	kamala	40	F	110	80	18.7	1.14	7	165	68	63	16.9	n	
16	muniamma53	53	F	120	80	21.1	1.2	8.16	167	58	60	16.3	n	
17	sankarapp	45	M	120	80	24.7	1.72	6.18	176	54	64	22.4	n	
18	anandi	28	F	120	70	20.7	1.23	7.9	156	60	54	16.6	n	
19	amuda	38	F	110	80	26.6	1.08	7.98	149	54	56	15.6	n	
20	ramu	41	M	120	90	27.2	1.22	13.4	164	58	60	17.8	n	