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Study on Diastolic Dysfunction in Rheumatoid Arthritis

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Abstract: *Aim: The aim of this study was to evaluate left ventricular diastolic dysfunction in patients with rheumatoid arthritis with special regard to disease activity and duration. Methods: 110 patients of seropositive Rheumatoid arthritis during the study period from January 2018 to July 2018 were included in the study. All patients were assessed using DAS 28 score for disease activity and transthoracic echocardiography using M-mode, 2D, conventional doppler echocardiography and TDI. Results: Using DAS 28 score patients were categorized into those with inactive disease (score <2.1) and those with active RA (score>2.1). Among conventional Doppler early diastolic flow velocity (E), late diastolic flow velocity(A) were measured. E/A was found to be lower in RA patients. From TDI parameters, e' (early diastolic), a'(late diastolic) annular velocities were measured and E/e' and e'/a' ratios were calculated. We found that e' was found to be lower in patients with RA and E/e' ratio was found to higher in RA patients consistent with diastolic dysfunction. There was a strong correlation between CRP positivity and diastolic dysfunction (p<0.05); disease activity also positively correlated with diastolic dysfunction. Conclusion: It is concluded that Rheumatoid arthritis patients in the absence of clinical evidence of heart disease show diastolic dysfunction. CRP and disease activity have a strong correlation with diastolic dysfunction. However we could not demonstrate any relation between the duration of disease and diastolic dysfunction.*

Keywords: Rheumatoid Arthritis , Diastolic dysfunction , DAS 28 Score.

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I. Introduction

Rheumatoid arthritis is the most common systemic autoimmune disease(1). Prevalance of Rheumatoid arthritis is 0.8% worldwide. Although RA is primarily considered a disease of the joints, abnormal systemic immune responses are evident and can cause a variety of extra-articular manifestations. Long term survival of patients with RA is shorter compared with that of general population or control subjects without RA(2).Several studies have documented increasing morbidity and mortality among patients with rheumatoid arthritis(2-4). Patients with RA have an apparent 2 fold higher incidence of congestive heart failure as compared to general population or controls without RA (5). CHF is an independent risk factor for mortality in RA and is responsible for 1 in 8 deaths of patients with RA (6). Cardiac failure in RA is the result of either systolic or diastolic dysfunction or both. The higher incidence of heart failure in RA necessitates the research of its precursor forms and pre clinical assessment, and therefore the importance of studying diastolic dysfunction in patients with RA. Diastolic dysfunction is usually attributable to common structural abnormalities such as hypertrophy or interstitial fibrosis and impaired relaxation(7).

A number of non invasive techniques like Doppler echocardiography , colour doppler M-mode, Tissue Doppler Imaging (TDI) , magnetic resonance imaging, and radionuclide ventriculography can be used for the evaluation of LV diastolic functions(8).Several studies reveal that diastolic velocity detected with Tissue Doppler Imaging is pre-load independent and it can be used with reasonable accuracy even in patients with tachycardia(9-11). The aim of this study was to evaluate LV diastolic dysfunction using TDI in addition to conventional Doppler in RA patients without apparent cardiovascular disease, with special regard to disease activity and duration.

II. Materials and Methods

This descriptive cross sectional study was carried out on outpatients attending Rheumatology OPD at Government Kilpauk Medical college & Hospital, Chennai, Tamilnadu from January 2018 to July 2018. A total of 110 patients, aged 18 – 60 years of either gender meeting the inclusion criteria were included in the study.

Study Population : patients affected by Rheumatoid Arthritis as diagnosed by 2010 ACR/EULAR

classification criteria were enrolled in the study(12)

Study Design : Descriptive cross sectional study

Study Location : This was a tertiary care teaching hospital based study done in Department of Rheumatology at Govt. Kilpauk medical college and Hospital, Chennai, Tamilnadu.

Study duration : January 2018-July 2018

Inclusion Criteria :

- Adults more than 18 years of age of either gender
- Seropositive Rheumatoid arthritis

Exclusion Criteria :

- Patients with H/o Cardiac disease
- Patients with H/o Diabetes mellitus
- Patients with H/o Hypertension
- Patients with H/o Chronic lung disease
- Patients with H/o chronic drug intake except anti rheumatic drugs
- Patients with H/o thyroid disorder
- Patients with ECG evidence of ventricular hypertrophy, Bundle branch blocks, dysrhythmy.
- Patients with H/o alcohol abuse
- Patients more than 60 years of age.

Procedure methodology

After obtaining informed consent, patients enrolled in the study underwent complete clinical and physical examination. Disease activity was analyzed using visual analog scale for pain and DAS28 questionnaire. Samples were also collected from patients for laboratory investigations including complete hemogram, ESR, CRP, Rheumatoid factor and Anti –CCP. Transthoracic Echocardiogram was performed by cardiologist blinded to clinical evaluation and treatment received.

Rheumatoid Factor was estimated by Nephleometry method and Anti CCP was determined by ELISA method. ESR was measured at the end of one hour by westegren's method. CRP was measured by Latex agglutination method using AVITEX kit manufactured by Omega Diagnostics.

Transthoracic echocardiogram was performed using Philips HD11 XE machine and 3.5 MHz electronic transducer. All echocardiographic evaluations were made in supine posture. M-mode and 2D imaging were performed, followed by Doppler. For mitral inflow, the sample volume was placed at the mitral valve tips in the apical four chambered view with recording of 5 cycles. Using TDI program, a 5 mm sample volume was placed at the mitral annulus in the 4- chamber view. Gains were adjusted to eliminate the background noise and allow for clear tissue signals. 5 cycles were recorded.

Simpson's biplane method was used to calculate ejection fraction of left ventricle using 2-D echocardiography(13). LV end- diastolic dimension (LVD), LV end-systolic dimensions(LVS), Left atrial dimension(LA) were measured with M-mode echocardiography using a parasternal view. Following parameters were measured using Doppler : peak of early diastolic(E) and late diastolic(A) flow velocity, E/A ratio, and deceleration time(DT) of flow velocity in early diastole. Using TDI following measurements were made from mitral annular velocity: early diastolic(e'), late diastolic (a') annular velocities and e'/a' and E/e' ratios. Doppler measurements were averaged over 5 consecutive cycles.

III. Statistical Analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference in the multivariate analysis the one way ANOVA with Tukey's Post-Hoc test was used. To find the significance in categorical data Chi-Square test was used. In both the above statistical tools the probability value of 0.05 is considered as statistically significant.

IV. Results

From January 2018 to July 2018 a total of 110 patients with Rheumatoid arthritis underwent Transthoracic echocardiogram for evaluation of diastolic dysfunction. 23% (n=25) were males and 77%(n=85) were females Fig1. Duration of rheumatoid arthritis less than 1 year were 15%(n=17) , between 1-3 years were 29%(n=32) , between 3-5 years were 37%(n=40), and above 5 years were 19%(n=21) fig2. DAS28 score <2.1 were considered to have inactive disease 34%(n=37), and DAS score > 2.1 were considered to have active RA 63%(n=73). CRP positivity was found in 70% (n=77) and was negative in 30%(n=33)Table1. Only 34 patients (30%) had normal diastolic function; 76 patients (70%) had various grades of diastolic dysfunction on echocardiogram fig3. Among patients with diastolic dysfunction 8 patients (10%) had grade 1, 29 patients

(38%) had grade 2 and 39 patients(52%) had grade 3 diastolic dysfunction. Our study showed positive correlation between CRP positivity and diastolic dysfunction($p<0.05$) table 2. With respect to disease activity ,those with higher DAS 28 score had a higher prevalence and greater grades of diastolic dysfunction Table 3 & Fig 4. We also found that diastolic dysfunction was present even within 1 year of onset of disease and duration of disease did not correlate with diastolic dysfunction Table 4 & fig 5.

Fig 1 : Shows Gender distribution among study population. 23 % were males and 77% were females.

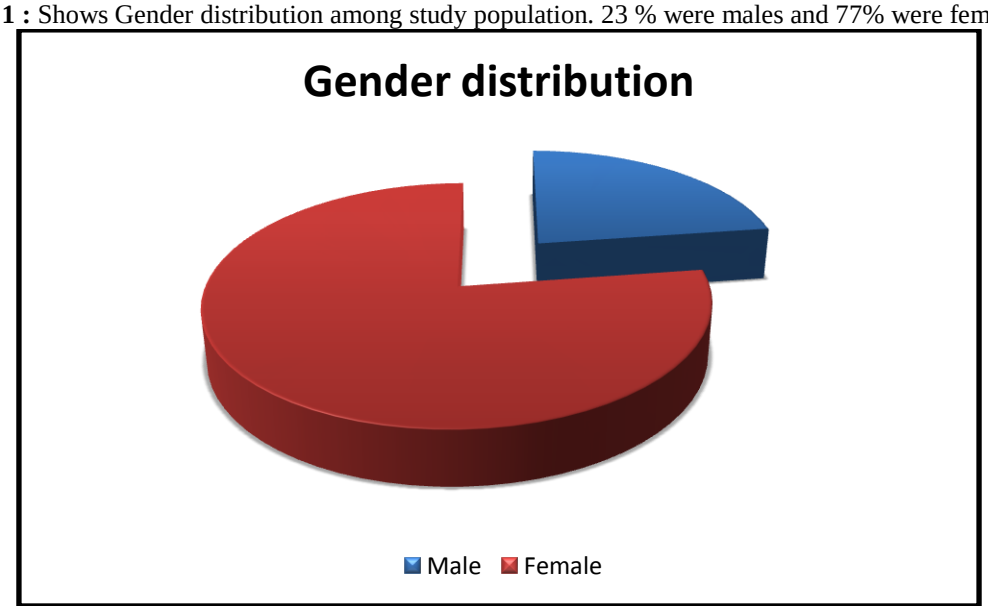


Fig 2 : Shows duration of Rheumatoid arthritis among study population.15%(n=17) were within 1 year; 29%(n=32)were between 1-3 years ; 37%(n=40) were between3-5 years ; 19% were above 5 years .

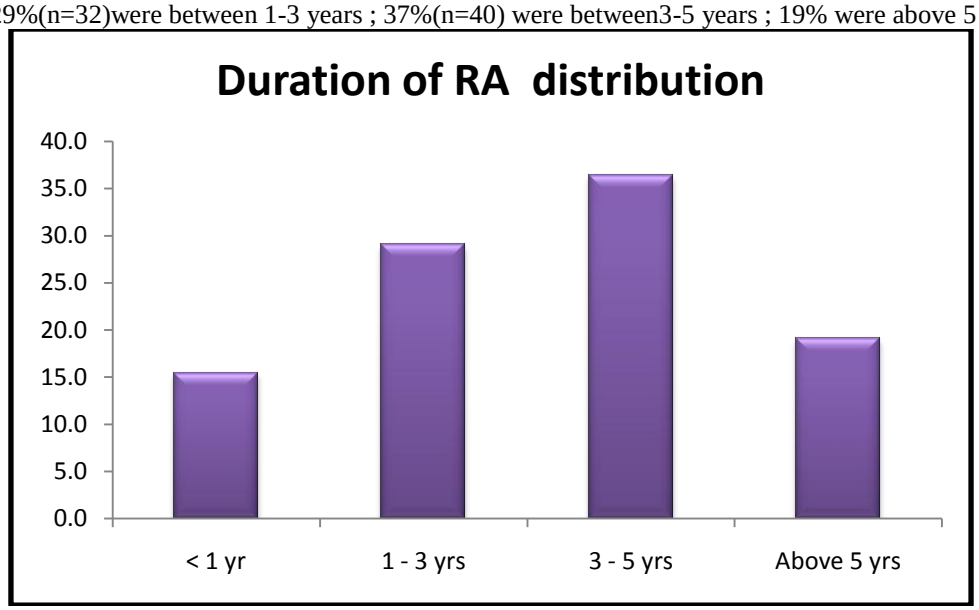


Table 1: Shows CRP positivity among study population. Value of 6 and 12 are considered positive

CRP

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	33	30.0	30.0	30.0
	6	54	49.1	49.1	79.1
	12	23	20.9	20.9	100.0
	Total	110	100.0	100.0	

Fig 3 : shows percentage of diastolic dysfunction among the study population. Only 30% of the population had normal diastolic function. 70% of population had various grades of diastolic dysfunction as depicted picture below.

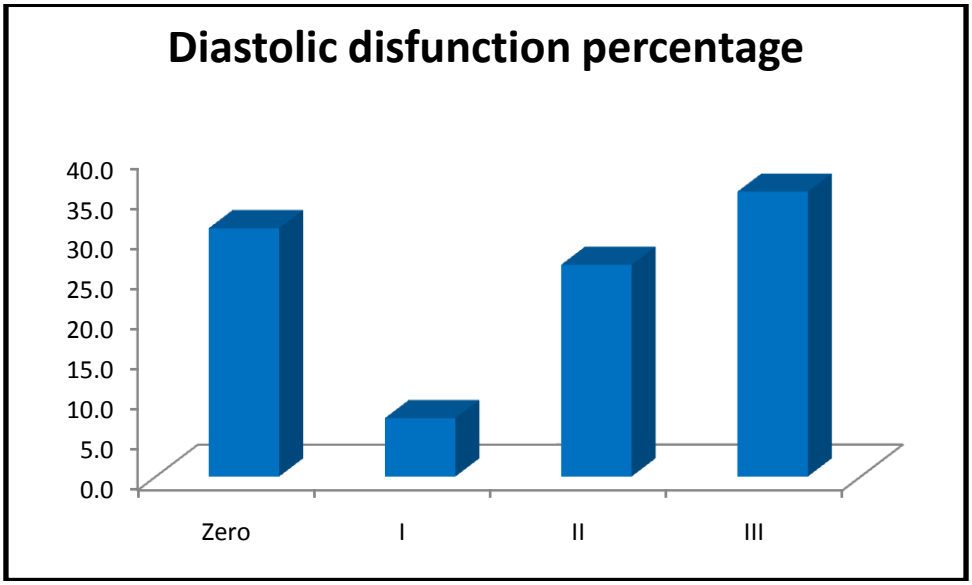


Table 2 : shows correlation between CRP positivity and diastolic dysfunction

Crosstab

			Grade				Total
			0	1	2	3	
CRP	0	Count	21	2	5	5	33
		% within Grade	61.8%	25.0%	17.2%	12.8%	30.0%
	6	Count	12	4	16	22	54
		% within Grade	35.3%	50.0%	55.2%	56.4%	49.1%
	12	Count	1	2	8	12	23
		% within Grade	2.9%	25.0%	27.6%	30.8%	20.9%
Total		Count	34	8	29	39	110
		% within Grade	100.0%	100.0%	100.0%	100.0%	100.0%

Fig 4 : Shows CRP positivity among various grades of diastolic dysfunction.30%(n=33) had negative CRP and 70%(n=77) had positive CRP values. Among those with positive CRP, Higher the CRP value,the greater is the diastolic dysfunction as depicted in the fig below.

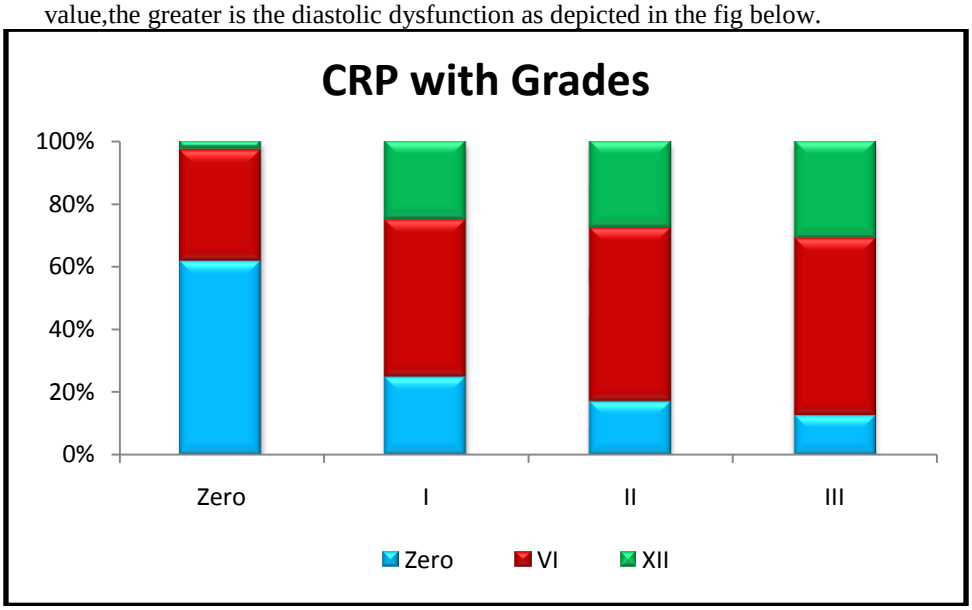


Table 3: Shows Correlation between DAS 28 Score and diastolic dysfunction.

DAS 28 * Grade

Crosstab

			Grade				Total
			0	1	2	3	
DAS 28	1	Count	26	3	6	2	37
		% within Grade	76.5%	37.5%	20.7%	5.1%	33.6%
	2	Count	6	1	10	9	26
		% within Grade	17.6%	12.5%	34.5%	23.1%	23.6%
	3	Count	2	4	11	14	31
		% within Grade	5.9%	50.0%	37.9%	35.9%	28.2%
	4	Count	0	0	2	14	16
		% within Grade	0.0%	0.0%	6.9%	35.9%	14.5%
Total		Count	34	8	29	39	110
		% within Grade	100.0%	100.0%	100.0%	100.0%	100.0%

Fig 4 : Shows that higher the disease activity, greater is the diastolic dysfunction.
DAS 28 score< 2.1 (inactive)- I(Blue) ; DAS 28 score 2.1-3.2 (Low)-II(Red);
DAS score 3.2-5.1(Moderate) – III(green) ; DAS 28Score >5.1 (High) – IV (Violet);

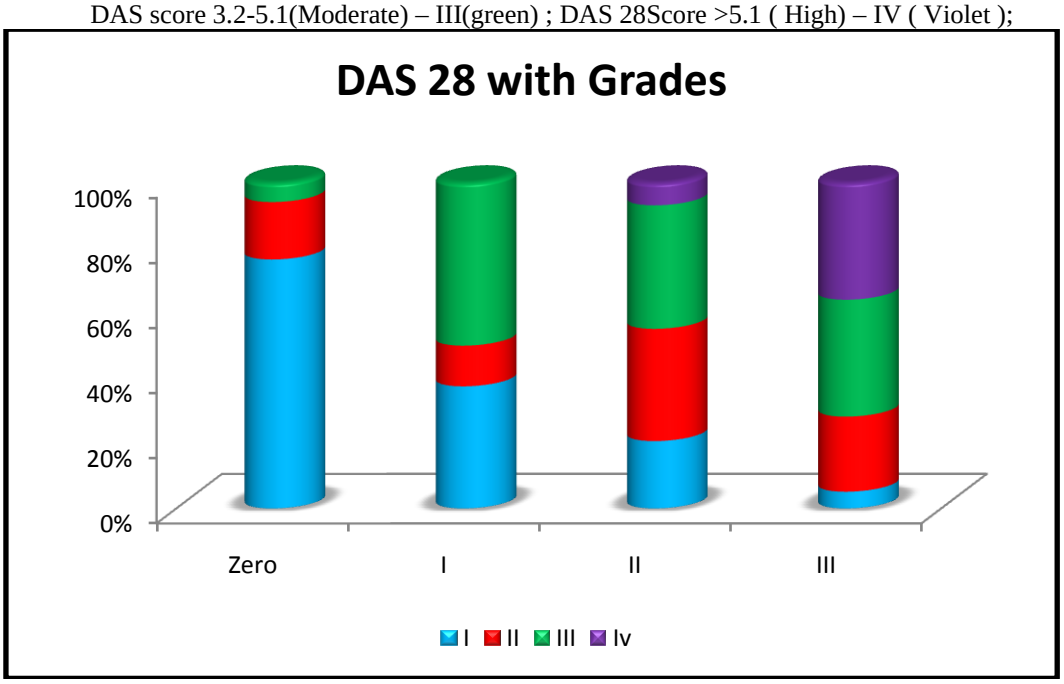


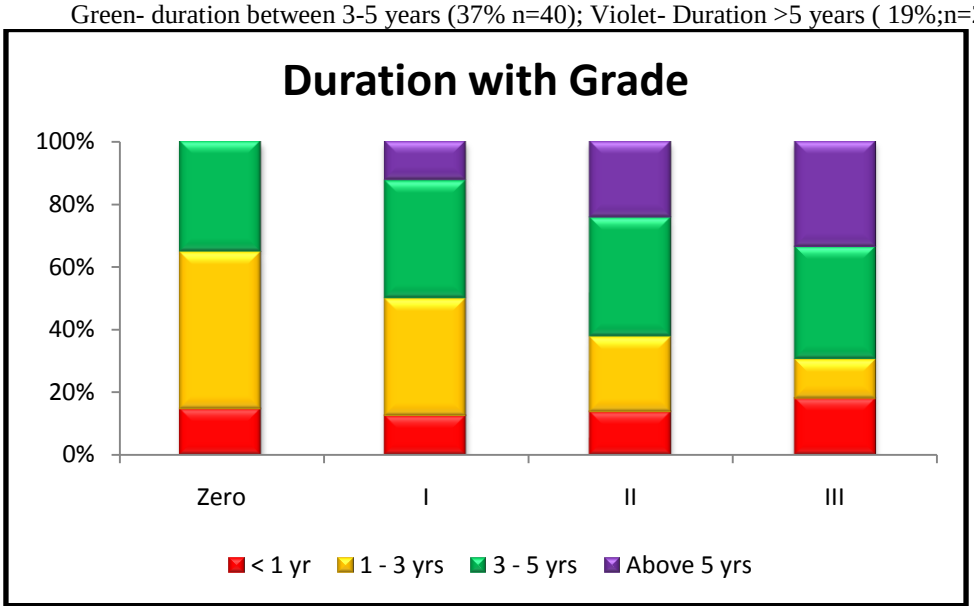
Table 4: Shows Duration of RA among the study population and various grades of diastolic dysfunction

Duration * Grade

Crosstab

			Grade				Total
			0	1	2	3	
Duration	< 1 yr	Count	5	1	4	7	17
		% within Grade	14.7%	12.5%	13.8%	17.9%	15.5%
	1 - 3 yrs	Count	17	3	7	5	32
		% within Grade	50.0%	37.5%	24.1%	12.8%	29.1%
	3 - 5 yrs	Count	12	3	11	14	40
		% within Grade	35.3%	37.5%	37.9%	35.9%	36.4%
	Above 5 yrs	Count	0	1	7	13	21
		% within Grade	0.0%	12.5%	24.1%	33.3%	19.1%
Total		Count	34	8	29	39	110
		% within Grade	100.0%	100.0%	100.0%	100.0%	100.0%

Fig 5 : Red- Duration within 1 year (16%; n=17). Yellow – duration between 1- 3 years (29% n=32) Green- duration between 3-5 years (37% n=40); Violet- Duration >5 years (19%;n=21)



V. Discussion

Rheumatoid Arthritis is the most common inflammatory arthritis, affecting 0.8%-1% of the general population. Cardiovascular diseases are common among RA patients. In a detailed study of rheumatoid patients using Echocardiography, Holter monitors and electrocardiography, it was reported that 70% of patients with nodular disease and 40% of those with non-nodular RA have some form of cardiac involvement, including valve thickening and incompetence(14).

Congestive cardiac failure is an independent risk factor for mortality among RA patients. The preservation of EF with the development of diastolic dysfunction suggests pathophysiologic mechanisms occurring primarily on the diastolic properties of hearts of patients with RA. The natural history of diastolic dysfunction in RA is not well known. Diastolic dysfunction in RA is usually attributable to common structural abnormalities such as interstitial fibrosis and impaired relaxation.(7)

A number of non invasive techniques like conventional Doppler echocardiography , M-mode colour Doppler , tissue Doppler imaging , magnetic resonance imaging and radio nucleotide ventriculography can be used for the evaluation of diastolic function(8). Mitral inflow velocities detected by conventional Doppler echocardiography are affected by several factors such as heart rate, preload and after load. Tissue Doppler imaging is a recent echocardiographic technique employing Doppler principle to measure the velocity of myocardial segments and other cardiac structures. Longitudinal myocardial fibre motion impairment is a sensitive marker of early myocardial dysfunction and ischemia, and TDI might therefore become an important tool in routine assessment. TDI has a great potentional in the diagnosis of left ventricular diastolic dysfunction, overcoming the load dependence of conventional Doppler techniques (9-11).

Several studies have measured E, A and E/A ratio from conventional doppler transvalvular mitral flow parameters for the evaluation of diastolic dysfunction in RA patients (15-18). From these parameters E/A ratio was found to be lower in patients with RA. The results obtained in our study was concordant with the literature. From TDI parameters, e'(early diastolic), a'(late diastolic) annular velocities were measured and E/e' and e'/a' ratios were calculated. We found that e' was lower and E/e' ratio was found to be higher in RA patients consistent with diastolic dysfunction and DD was graded as per ASE (American society of echocardiography) recommendations.

Inflammation may accelerate atherosclerosis, thrombosis and congestive cardiac failure(19). In our study the disease activity was assessed using DAS28 score. DAS 28 score less than 2.1 were considered to be in remission and those with DAS28 score more than 2.1 were considered to have an active disease. We found a positive correlation between disease activity and diastolic dysfunction, which was consistent with literature (20). Consequently we also found that diastolic dysfunction was present even with disease onset and that the duration of disease did not correlate with diastolic dysfunction.

VI. Conclusion

Our study concluded that Rheumatoid arthritis patients in the absence of clinical evidence of heart disease show diastolic dysfunction. CRP and disease activity have a strong correlation with diastolic dysfunction in RA patients. However we could not demonstrate any relation between the duration of disease and diastolic dysfunction.

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