Research Article

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Left atrial function in rheumatoid arthritis patients

Background: The left atrium modulate left ventricular filling and plays a role in maintaining overall cardiac function during left ventricular ischemia by reactive hyperactivity, Cardiovascular disease is recognized as the leading cause of death in RA patients. Methods and Findings: 30 healthy control, & 45 RA patient subjected to full clinical assessment, DAS 28 ESR score, full laboratory evaluation, conventional and tissue Doppler imaging (TDI) and strain (S) and strain rate (SR) analysis by two-dimensional speckle tracking of the left atrium. We found statistically significant difference in 2 Left atrial PEF, 2 Left atrial EI, 2 Left atrial TEF, TDI mitral lateral annulus e', TDI mitral lateral annulus S, Average SR E 1/s between patients and controls,& negative correlation between TDI lateral e, TDI lateral s, and Strain rate e and rheumatoid factor, There was negative correlation between 2LA PEF, 2LA EI, and 2LA TEF . Rheumatoid factor is correlated to strain rate e, and negatively correlated with left atrial passive emptying. Conclusion: RA had alteration in left LV longitudinal myocardial function, left atrial expansion volume can be a predictor of AF in RA. RA patient had more left atrial stiffness. Our study concluded cardiac affection is more in seropositive RA patients.

Keywords: RA ● echocardiography ● tissue Doppler ● left atrial function

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Introduction

Rheumatoid arthritis (RA) is a common autoimmune systemic inflammatory disease affecting approximately 1% of the worldwide population. Interaction of genetic and environmental factors results in a cascade of immune reactions, which ultimately lead to the development of synovitis, joint damage, and structural bone damage [1].

Patients with RA are at a twofold increased risk for myocardial infarction and stroke, with risk increasing to nearly threefold in patients who have had the disease for 10 years or more. Congestive heart failure appears to be a greater contributor to excess mortality than ischemia in those patients. This increased cardiovascular disease risk in RA patients seems to be independent of traditional cardiovascular risk factors. Pathogenic mechanisms include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms such as T-cell activation that subsequently lead to endothelial dysfunction, a decrease in endothelial progenitor cells, and arterial stiffness, which are the congeners of accelerated atherosclerosis observed in RA patients [2].

Multiple studies have shown that accelerated and increased atherosclerosis in autoimmune diseases leads to ischemic coronary artery disease. The proposed mechanisms for this are a major systemic inflammatory state involving T cell lymphocytes, tumor necrosis factor alpha (TNF alpha), high density lipoprotein dysfunction, and treatment related hyperhomocysteinemia. All these factors lead to thickening of arterial intima, myocardial dysfunction, and in some cases myocardial infarction and are responsible for up to 50% of deaths in this population [3]. RA has been linked to several structural heart abnormalities, including increased right ventricular filling pressure, left ventricular hypertrophy, pulmonary artery hypertension, and as much as twice the prevalence of heart failure [4].

The importance of the left atrium in cardiovascular performance has long been acknowledged. Quantitative assessment of left atrial (LA) function is laborious, requiring invasive pressure-volume loops and thus precluding its routine clinical use. In recent years, novel post-processing imaging methodologies have emerged, providing a

complementary approach for the assessment of the left atrium. Atrial strain and strain rate obtained using either Doppler tissue imaging or two-dimensional speckle-tracking echocardiography has proved to be feasible and reproducible techniques to evaluate LA mechanics [5].

Objectives

The left atrium modulates left ventricular filling, CVS is recognized as a leading cause of death in RA patients, so we try to find a noninvasive method to detect early affection, even with no clinical manifestation.

Methodology

Our study included 45 Rheumatoid arthritis patients from the outpatient clinic of Rheumatology and Immunology and inpatients of internal medicine department, in Kasr al Aini university hospital. They were diagnosed rheumatoid arthritis according to the revised classification criteria of the American College of Rheumatology 1987, and 30 normal subjects age- and sex matched volunteers.

An informed oral consent was taken from all participants.

Local ethical committee approval was taken.

All patients were subjected to full clinical history and examination, with special emphasis on rheumatoid activity, and cardiovascular manifestation.

Laboratory investigation in the form of CBC, ESR, rheumatoid factor was done to all participants.

DAS 28 ESR was calculated to all rheumatoid arthritis patients. The DAS28 [6] is based on a count of 28 swollen and tender joints, together with the ESR and then enter this data in special calculator, with a score ranging from 0 to 9.4 [7].

Echocardiographic examination

The entire study population was subjected to transthoracic echocardiography, including conventional and tissue Doppler imaging (TDI) and strain (S) and strain rate (SR) analysis by two-dimensional speckle tracking of the left atrium. Images were obtained using an Esaotemy lab 50 with a 2.5 MHz sector transducer equipped with the TDI mode and speckle tracking.

Conventional Echocardiographic measurements

Left ventricular dimensions: These included LV end diastolic dimension and LV end systolic dimension.

Left ventricular ejection fraction (EF): This was estimated using the biplane Simpson's method in the four-chamber and two chamber views.

Left atrial volumes: From apical 4- and 2-chamber views, 3 separate LA volumes have been measured in each view, according to the American Society of Echocardiography guidelines and using biplane modified Simpson's method of discs. Volumes were indexed to body surface area as recommended.

- LA maximum volume (V max): measured at end systole, the time at which the atrial volume is the largest just before MV opening (at the end of the T wave of the ECG).
- LA minimum volume (V min): measured at end diastole, the time at which the atrial volume is at its nadir just before MV closure (at the QRS of the ECG). Before atrial contraction volume (V pre -A): is estimated as the last frame before mitral valve reopening (at the onset of the P wave on ECG).

Left atrial emptying fractions

These were derived from indexed LA volumes by the following formulas:

- LA passive emptying fraction (PEF): 100x [(V max/BSA)– (V Pre-A/BSA)) / (V max/BSA)].
- LA active emptying fraction (AEF): 100x [(V Pre-A/BSA) – (V min/BSA)) / (V Pre-A/BSA)].
- LA expansion index (EI): 100 x [((V max/BSA-V min/BSA)) / (V min/BSA)]
- LA total emptying fraction (TEF):100x [((V max/BSA)- (V min)/BSA)) / (V max/BSA)] X

Tissue Doppler imaging

TDI –derived mitral annular velocities: Mitral annular velocities were evaluated by TDI in the apical four chamber view. Peak velocities of the early (e') and late (a') diastolic phases and systolic (s) wave of the septal and mitral annulus were measured.

Left atrium electromechanical times: This was assessed by the following time intervals

- P-A start interval (from the onset of the P-wave to the onset of A′).
- P-A peak interval (from the onset of the P-wave to the peak of A′).
- Total electromechanical time (from the onset of the P-wave to the end of A′).

Two-Dimensional Speckle Tracking Strain and Strain Rate Analysis

For speckle tracking analysis, apical four-, two-, chamber

views were recorded. For each view, adequate gray scale images were obtained to outline the endocardial border of the LA. At least three consecutive cardiac cycles were acquired during which the patients held breathe following complete exhalation, and with a stable electrocardiographic recording.

Speckle-tracking analysis was performed offline using a commercially available semi-automatic two – dimensional strain software (Mylab 50, Esaote, Italy). For each analysis, the endocardial border was traced manually, in apical 4 chamber and apical 2 chamber at the end of systole with possibility of further correction.

Lastly strain and strain rate curves were generated for each atrial segment by the software. The region of interest was then divided into six segments and labeled as acceptable or unacceptable based on adequate tracking quality. In poor tracking segments, the endocardial trace line was able to be adjusted until improved tracking quality was achieved, from the three cycles the most typical curve was taken for the analysis. The left atrium was divided into 6 equidistant segments in each of the four-chamber and two-chamber views. The dedicated software generated automatically longitudinal LA strain and strain rate curves; and the following parameters were measured:

LA strain parameter

- Peak atrial longitudinal strain (PALS)
- 2-LA strain rate parameters:
- Peak atrial longitudinal strain rate during ventricular systole (SRs).
- Peak atrial longitudinal strain rate during early ventricular diastole (SR e).
- Peak atrial longitudinal strain rate during late ventricular diastole (SR a).
- SR s, SR e, and SR a indicate LA reservoir, conduit and booster pump function.
- All these parameters were calculated as the average of twelve segmental values in apical four and apical two chamber views

Results

Rheumatoid arthritis duration in our patients ranges from 1 to 25 years, with mean of 7.28 ±6.18 years, DAS 28 range from 2.4 to 5.9 with mean of 4.07 ±0.85 (Table 1).

There was no statistically significant difference in LVEDD, LVESD, EF, Apical 4 Volume max, Apical 4 Volume min, Apical 4 Volume pre a, Apical 2 Volume max, Apical 2 Volume min, 4 Left atrial PEF, 4 Left atrial AEF, 4 Left atrial EI, 2 Left atrial AEF, TDI mitral medial annulus e',TDI mitral medial annulus a', TDI medial annulus S ,TDI mitral lateral annulus a', Global PALS %, Average TTP strain, Average TTP SR E, Average SR A, Average TTP SR A, Average SR S, Average TTP SR S, Average TTP SR E,Average SR A (1/s), Average TTP SR A , Average SR S 1/s , Average TTP SR Sbetween patients and control (Tables 2-4).

There was statistically significant difference in 2 Left atrial PEF, 2 Left atrial EI, 2 Left atrial TEF, TDI mitral lateral annulus e', TDI mitral lateral annulus S, Average SR E 1/s between patients and controls with P value 0.01,0.09,0.02,0.001,0.02, 0.000 respectively (Tables 2-4).

There was no correlation between TDI lateral e, TDI lateral s, and Strain rate e and DAS 28, disease duration, different medication, either with doses or drug duration (Table 5).

There was negative correlation between TDI lateral e, TDI lateral s, and Strain rate e and rheumatoid factor, with P value 0.00, 0.05, 0.02 respectively (Table 5).

There was no correlation between 2LA PEF, 2LA EI, and 2LA TEF and DAS 28, disease duration, different medication, either with doses or drug duration (Table 6).

There was negative correlation between 2LA PEF, 2LA

Table 1. Clinical, laboratory and therapeutic data of rheumatoid arthritis patients.

Variable	Mean	Std. Deviation	Minimum	Maximum	Median
Duration of disease (years)	7.28	6.18	1	25	5
DAS 28	4.07	0.85	2.4	5.9	4
ESR	49.98	29.752	10	130	40
Methotrexate dose (mg)	19.06	4.00	10	25	18.75
Methotrexate duration (yrs.)	3.7375	3.25	0	13	2.5
Prednisolone dose (mg)	5.80	1.18	5	8	5
Prednisolone duration (yrs.)	3.66	3.27	1	15	2
Leflunomide dose(mg)	20	0	20	20	20
Leflunomide duration (yrs.)	3.66	2.16	1	7	3.5

Table 2. Comparison between patients and controls in different echo findings.			
Variable	**Group 1 patients No (45)**	**Group 2 control No (30)**	**p- value**
LVEDD (cm)	4.73±0.51	4.62±0.49	0.3
LVESD (cm)	3.14±0.37	3.05±0.44	0.3
EF%	60.91±5.9	61.46±5.04	0.6
Variable	Group 1 (N=45)	Group 2 (N=30)	p- value
Left atrial indexed volumes (ml/m²)			
Apical 4 Volume max	24.91	24.31	0.5
Apical 4 Volume min	10.48	9.78	0.50
Apical4 Volume pre-a	16.477	15.633	0.539
Apical 2 Volume max	22.22	23.34	0.3
Apical 2 Volume min	10.425	9.403	0.47
Apical2 Volume pre-a	15.19	13.753	0.30
Left atrial volume fraction indices (%)			
4 Left atrial PEF	35.46	38.9	0.24
4 Left atrial AEF	36.26	36.26	1.0
4 Left atrial EI	157.17	171.83	0.5
4 Left atrial TEF	57.06	59.73	0.3
2 Left atrial PEF	32.95	40.2	**0.01**
2 Left atrial AEF	36.04	39.63	0.29
2 Left atrial EI	144.11	194.73	**0.009**
2 Left atrial TEF	56.66	62.46	**0.025**
Data are presented as mean and standard deviation. max: maximum, mini: minimum, PEF: passive emptying fraction AEF: active emptying fraction, EI; expansion index. TEF: total emptying fraction.			

Table 3. Tissue Doppler imaging characteristics of the studied population.			
Variable	**Group 1 patients No (45)**	**Group 2 control No (30)**	**p- value**
TDI – derived mitral annular velocities (Cm/sec)			
TDI mitral medial annulus e'	11(7-18)	12(8-17)	0.30
TDI mitral medial annulus a'	10(7-16)	10(7-18)	0.10
TDI medial annulus S	10 (7-16)	10 (8-14)	0.92
TDI mitral lateral annulus e'	13(9-20)	15(13-19)	**0.001**
TDI mitral lateral annulus a'	11(7-17)	10(8-16)	0.31
TDI mitral lateral annulus S	10(7-16)	11(8-16)	**0.02**
Left atrial electromechanical times (m/sec)			
Time to A onset	84.32 (50-108.5)	82.3(53-119.5)	0.54
Time to A Peak	146.1(92-186)	148.76(102.5-208.5)	0.56
Time to A End	211.37(180.5-2580	207.75(152.5-279.5)	0.50
A Duration.	84.01(61-114)	82.76(106-80)	0.69

Table 4. Average TTP SR Sbetween patients and control.			
Global PALS %	56.02±17.56	63.76±22.48	0.09
Avrg TTP strain (msec)	413.93±40.20	420.32± 35.59	0.48
Avrg SR E 1/s	-2.45±0.61	-3.22 ±1.04	**0.000**
Avrg TTP SR E (msec)	525.05±39.05	534.87±47.98	0.33
Avrg SR A (1/s)	-2.53±0.81	-2.31±0.95	0.29
Avrg TTP SR A (msec)	731.36±85.06	760.08±80.62	0.14
Avrg SR S 1/s	2.62±0.60	3.52±3.71	0.11
Avrg TTP SR S (msec)	176.02±40.58	167.76±42.95	0.40
Data are presented as mean ± SD or number (percent).Avrg PALS=average peak atrial longitudinal strain, Avrg SR S=average strain rate S, Avrg SR E=average strain rate E, Avrg SR A=average strain rate A, Avrg TTP strain=average time to peak strain, Avrg TTP SR S=average time to peak strain rate S, Avrg TTP SR E=average time to peak strain rate E, Avrg TTP SR A=average time to peak strain A.			

EI, and 2LA TEF and rheumatoid factor, with P value 0.03, 0.04, 0.02 respectively (Table 6).

Statistical analysis

Data were statistically described in terms of mean

Table 5. Correlation between TDI, strain rate e, and clinical and laboratory and medication parameters.						
Variable	**TDI lateral e**		**TDI lateral s**		**Strain rate e**	
	R	**P**	**R**	**P**	**R**	**P**
Clinical data						
Age	-0.1	0.35	0.06	0.55	-0.06	0.60
Dis. Dur.	-0.04	0.78	0.14	0.35	-0.19	0.21
DAS 28	0.06	0.67	-0.15	0.32	-0.21	0.14
Laboratory data						
RF	-0.37	**0.00**	-0.21	0.05	-0.35	**0.002**
Medications data						
MTX dose	-0.18	0.30	-0.09	0.60	-0.33	0.06
MTX duration	-0.14	0.42	0.04	0.81	0.06	0.72
Prednisolone dose	0.03	0.86	0.07	0.70	-0.20	0.28
Prednisolone duration	0.10	0.58	0.12	0.52	-0.07	0.70
Leflunomide Duration	-0.31	0.53	0.31	0.53	0.33	0.52
*Dis Dur: disease duration, DAS 28; disease activity score system ESR 28, RF; rheumatoid factor, MTX; methotrexate.						

Table 6. correlation between left atrial volume fractions and clinical and laboratory and medication parameters.						
Variable	**2LA PEF**		**2LA EI**		**2LA TEF**	
	R	**P**	**R**	**P**	**R**	**P**
Clinical data						
Age	0.015	0.19	0.1	0.35	0.12	0.28
Disease duration	0.10	0.50	-0.01	0.9	0.11	0.45
DAS 28	0.009	0.9	0.04	0.79	-0.02	0.85
Laboratory data						
RF	-0.24	**0.03**	-0.23	**0.04**	-0.26	**0.02**
Medications data						
MTX dose	-0.11	0.53	0.04	0.79	-0.00	0.9
MTX dur	0.08	0.62	-0.06	0.71	0.00	0.99
Prednisolone dose	0.29	0.13	0.13	0.49	0.02	0.9
Prednisolone duration	-0.12	0.54	-0.16	0.40	-0.09	0.6
Leflunomide Duration	0.5	0.27	0.08	0.86	0.3	0.56
2LA PEF; Apical 2 left atrial passive emptying fraction, 2LA EI; Apical 2 expansion index. 2LA TEF; Apical 2 total emptying fraction, DAS 28; disease activity score system ESR 28, RF; rheumatoid factor, MTX; methotrexate.						

± standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation.

Discussion

It is now well established that RA is associated with increases in both morbidity and mortality compared with the general population. RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population [8] and CV disease (CVD) is the leading cause of death in RA patients [9]. Large retrospective studies of RA patients have shown the risk for myocardial infarction (MI), adjusted for CV risk factors, to be increased by up to 2-fold compared with control groups [10].

Pulsed-wave TDI is used to measure peak myocardial velocities and is particularly well suited to the measurement of long-axis ventricular motion because the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam in the apical views. Because the apex remains relatively stationary throughout the cardiac cycle, mitral annular motion

is a good surrogate measure of overall longitudinal left ventricular (LV) contraction and relaxation [11].

In our study there was inversely correlation between TDI peak early ventricular diastolic velocity, and lateral peak ventricular systolic velocity and the rheumatoid factor, and there was no correlation between DAS 28, disease duration, and different medications, which mean that rheumatoid arthritis patients irrespective of disease duration, and disease activity had alternation in LV longitudinal myocardial function parameters, also left ventricular contraction and relaxation affection not related to steroid intake, nor disease modifying drugs.

LA "passive emptying" is the decrease in LA volume from mitral valve opening to before the onset of LA systole normalized to the maximum LA volume. This change in volume reflects the early diastolic LV filling [12].

In our study there was statistically significant difference between patient and controls in left atrial passive emptying, with no correlation to disease activity, but inversely correlated to rheumatoid factor.

The LA expansion index predicts adverse events in patients with dyspnea. The prognostic power of the index exceeds that of other well-established echocardiographic parameters such as E/e' and maximal indexed LA volume [13]. Also Left atrial expansion index independently predicts post-CABG AF and in-hospital mortality [14].

Hsiao et al., 2013 study concluded that The LA expansion index is associated with the presence of AF, and a reduced LA expansion index has a strong association with persistent AF [15].

In our study there was no statistically significant difference between patient and controls in left atrial expansion volume, with no correlation to disease activity, but it is inversely correlated to rheumatoid factor, and this raise the importance of echocardiography in rheumatoid arthritis patients especially with those with high titer rheumatoid factor, as this may be an early predictor factor for atrial fibrillation in this patients.

Strain rate (SR) imaging provide data on myocardial deformation by estimating spatial gradients in myocardial velocities. The use of LA strain imaging has been examined in several clinical scenarios. LA strain during atrial systole is significantly reduced in diastolic HF patients secondary to LA stiffness [16].

In our study there was statistically significant difference in Average SR E 1/s between patients and controls, which denote more left atrial stiffness in patients with rheumatoid arthritis, and there was statistically significant correlation between Strain rate e and rheumatoid factor.

Conclusion

RA had alteration in left LV longitudinal myocardial function despite rheumatoid activity or disease duration. Left atrial expansion volume can be a predictor of AF in RA. RA patient had more left atrial stiffness. Rheumatoid factor is correlated to strain rate e, and negatively correlated with left atrial passive emptying, denoting more cardiac affection in rheumatoid arthritis patients than seronegative ones.

Conflict of interest

None

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