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Can myocardial dysfunction be detected in patients with rheumatoid arthritis with no cardiac symptoms?

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Abstract. – OBJECTIVE: The aim of our study was to investigate the role of tissue Doppler and Myocardial Performance Index (MPI) in evaluating cardiac involvement in patients with rheumatoid arthritis (RA) with no cardiac symptoms, to determine whether these measurements differ between healthy controls and RA patients, and whether they can be used to determine the risk of cardiovascular disease and predict prognosis.

PATIENTS AND METHODS: 50 RA patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA criteria and 50 healthy volunteering controls were included in the study. All patients and controls were assessed using electrocardiography (ECG), echocardiography, conventional Doppler echocardiography and tissue Doppler echocardiography. MPI values were calculated. In addition, RA patients were compared after being divided into two subgroups: seropositive and seronegative RA. Disease activity levels of the patients were determined based on Disease Activity Score in 28 Joints (DAS28).

RESULTS: The control group and RA group were compared in terms of PR interval, left atrial diameter, E/A, E/e', and MPI values. Comparisons between the groups yielded statistically significant differences in left atrial diameter, E/A, E/e', and MPI values and no significant difference in PR intervals. These parameters were also compared between seropositive and seronegative patients. Left atrial diameter was significantly higher in seronegative patients than in seropositive patients. There was no significant difference in the other values. DAS28 scores had no correlation with cardiac parameters.

CONCLUSIONS: Early detection of ventricular dysfunction in RA may be useful in clinical practice when predicting prognosis and optimizing treatment. The present study found that RA patients had impaired tissue Doppler measurements and MPI results compared to controls. MPI and tissue Doppler may be useful in early detection of ventricular dysfunction.

Key Words:
Rheumatoid arthritis, Myocardial performance index (MPI), Tissue doppler.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease with articular and non-articular involvement affecting synovial joints. This disease can affect any cardiac structure (valves, myocardium, endocardium, pericardium, conduction system, and coronary arteries), leading to various clinical manifestations such as myocarditis, pericarditis, myocardial fibrosis, arrhythmias, coronary artery disease, pulmonary hypertension, valvular disease, and heart failure. Given that all of these involvements are associated with poor prognosis, it is important to determine subclinical cardiac involvement in RA patients[1]. Early detection and treatment of subclinical cardiac involvement may restrict long-term morbidity and mortality.

Seropositivity (positivity for rheumatoid factor and/or anti-citrullinated peptide antibodies) is a prognostic factor in rheumatoid arthritis and is connected with radiographic progression. Former studies[2-4] have shown differences in the pathogenesis of anti-citrullinated peptide antibody (Anti-CCP)-positive and negative disease. Anti-CCP- and RF-positivity is associated with elevated inflammatory activity and is implicated in the pathogenesis of atherosclerosis and cardiac involvement[5].

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Conventional Doppler (pulse-wave Doppler) echocardiography has been shown to be useful in evaluating ventricular function in patients with RA[2]. However, this standard non-invasive technique is influenced by several factors including left atrial pressure, myocardial relaxation velocity, and volume status[6].

Tissue Doppler echocardiography is an echocardiographic technique that measures the velocity of myocardial segments. It also measures the velocity of other cardiac structures. This technique allows quantitative measurement of regional myocardial function. It is used for the early diagnosis of left ventricular diastolic dysfunction in cases where conventional Doppler echocardiography is insufficient[7]. Compared to conventional Doppler echocardiography, this technique is relatively less influenced by factors such as left atrial pressure, myocardial relaxation velocity, and volume status[8,9].

The myocardial performance index (MPI) is calculated using cardiac time intervals obtained by tissue Doppler technique. It is calculated using the sum of isovolumic contraction time and isovolumic relaxation time (IVRT) divided by ejection time. It is a tissue Doppler index that allows combined assessment of systolic and diastolic MPI in patients with systolic dysfunction. It assesses the global function of the ventricles and is not affected by preload and afterload changes[10].

It is important to detect cardiac involvement in the asymptomatic stage in RA. To the best of our knowledge, although there are studies[11,12] in the literature on tissue Doppler examinations in RA patients, there is very little research[13] on MPI. Investigating the importance of MPI in RA may be important. The aim of this study was to investigate the role of tissue Doppler examinations and MPI in the assessment of cardiac involvement in RA patients with no cardiac symptoms and to investigate whether these measurements can be used to determine the risk of cardiovascular disease and predict prognosis.

Patients and Methods

The study included 50 RA patients aged 18-60 years who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA diagnostic criteria[14] and 50 healthy volunteering controls. Patients were included if they had no known history of diabetes mellitus, hypertension, cardiovascular disease, renal failure, pulmonary disease, hypercholesterolemia, smoking, and had an ECG with normal sinus rhythm. Cardiac assessment was performed using a 12-lead electrocardiogram (ECG). PR interval was calculated as time interval from onset of the P wave to onset of the QRS complex on the ECG. Echocardiographic images were obtained for all subjects using a 1.5-4.5 MHz probe with GE Vivid T8 echocardiography device. Left atrial diameters were measured. Left ventricular ejection fraction was calculated using the Modified Simpson's rule[15]. In addition to conventional echocardiography measurements, conventional Doppler and tissue Doppler examinations were performed. Conventional Doppler examination was performed to measure early diastolic filling velocity (E wave), diastole, and late diastolic filling velocity (A wave) in all cardiac cycles, and these values were used to calculate the E/A ratio.

Tissue Doppler measurements were performed in an apical 4-chamber view at the septal and lateral tip of the mitral valve. Early diastolic peak velocity (e'), late diastolic peak velocity (A'), and peak systolic velocity (S) were measured three times in sequence and were averaged. Mitral E/e' ratio was calculated.

Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) levels of the patients were measured. Disease activities were calculated using the Disease Activity Score in 28 Joints (DAS28) based on the number of swollen and tender joints, serum CRP levels, overall assessment of the patient, and Visual Analog Scale (VAS) scores[16].

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 statistical program (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation and categorical variables were expressed in percentage. Continuous variables in both groups were compared using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test. Statistical significance was set at $p < 0.05$. Pearson correlation test was used for correlation analysis.

Results

RA patients had a mean age of 46.54 ± 9.31 years and a mean BMI of 26.40 ± 3.67; and the control group had a mean age of 43.42 ± 12.02

years and a BMI of 25.6 ± 3.23. There was no statistical difference between patients and controls in terms of mean age and BMI. 39 (78%) of the patients were female and 11 (22%) were male; 32 (64%) of the controls were female and 18 (36%) were male. No significant difference was noted in sex distributions. The mean disease duration in RA patients was 10.77 ± 8.52 years. Of the patients, 35 (70%) were seropositive and 15 (30%) were seronegative. There was no RF positivity in the control group. 15 (30%) of the patients had a history of using biologic agents (Table I).

The patients had a mean CRP value of 9.49 ± 8.39 mg/dl, mean ESR of 25.78 ± 16.62 mm/h and mean DAS28 score of 2.98 ± 0.36 (Table II).

When the patients and controls were compared in terms of PR interval, left atrial diameter, E/A, E/e', and MPI values, a significant difference in left atrial diameter, E/e', E/A, and MPI values, and no significant difference in PR intervals was observed (Table III).

In the RA group, seronegative patients had a significantly higher left atrial diameter than the seropositive patients and there was no significant difference in E/A, E/e', and MPI values (Table IV).

Analysis of the correlation of disease duration with PR interval, left atrial diameter, E/A, E/e', and MPI values found that disease duration had a significant positive correlation with E/e' and a significant negative correlation with left atrial diameter and PR interval. Analysis of the correlation of DAS28 with PR interval, left atrial diameter, E/A, E/e', and MPI values found no significant correlation (Table V).

Discussion

RA patients have a lower life expectancy compared to the normal population due to increased cardiovascular morbidity[17]. Cardiovascular involvement in RA has been shown to be similar to cardiovascular involvement in diabetes mellitus. Clinical

Table I. Demographic and clinical characteristics of the patients and controls.

	Patients	Controls	p
Age (years)	46.54 ± 9.31	43.42 ± 12.02	0.150
BMI (kg/m²)	26.4 ± 3.67	25.6 ± 3.23	0.266
Sex distribution (Female, %)	78	64	0.123
Seropositivity (%)	70	-	-
Duration of disease (years)	10.77 ± 8.52	-	-
Use of biological agents (%)	30	-	-

Table II. Mean ESR, CRP, and DAS28 levels in the patients.

	Patients
ESR (mm/h)	25.78 ± 16.62
CRP (mg/dl)	9.49 ± 8.39
DAS28	2.98 ± 0.36

Table III. PR interval, left atrial diameter, E/A, E/e', and MPI values in the patients and controls.

	RA patients	Controls	p-value
PR interval (ms)	152.06 ± 20.93	146.90 ± 15.95	0.184
Left atrial diameter (mm)	31.96 ± 3.40	30.08 ± 3.56	**0.008**
E/A	0.92 ± 0.24	1.21 ± 0.35	**0.000**
E/e'	8.21 ± 2.52	7.21 ± 2.11	**0.034**
MPI	0.67 ± 0.18	0.47 ± 0.05	**0.000**

Table IV. PR interval, left atrial diameter, E/A, E/e' and MPI values in seropositive and seronegative patients.

	Seropositive patients	Seronegative patients	*p*-value
PR interval (ms)	153.85 ± 23.61	147.86 ± 12.36	0.257
Left atrial diameter (mm)	31.14 ± 3.38	33.86 ± 2.66	**0.008**
E/A	0.90 ± 0.25	0.96 ± 0.22	0.518
E/e'	8.26 ± 2.45	8.28 ± 2.73	0.983
MPI	0.67 ± 0.17	0.66 ± 0.21	0.596

Table V. Correlation of DAS28 and disease duration with PR interval, left atrial diameter, E/A, E/e', and MPI values.

		DAS28	Duration
Left atrial diameter (mm)	r	-0.042	**-0.333**
	P	0.773	**0.018**
E/e'	r	-0.072	**0.303**
	P	0.618	**0.033**
E/A	r	0.235	0.196
	P	0.100	0.172
MPI	r	0.173	-0.071
	P	0.228	0.622
PR interval (ms)	r	-0.134	**-0.281**
	P	0.355	**0.048**

presentation and preclinical atherosclerosis of the two are similar[18,19]. RA patients are less likely to report symptoms of angina compared to the general population, may have silent myocardial infarction, and have higher mortality rates from acute coronary syndromes than those in general population, like in the case of diabetes mellitus[20]. These findings show the need for detailed cardiac screening before cardiac involvement becomes clinically evident or progresses to irreversible stages.

PR interval on an ECG is measured as time interval from the onset of the P wave to the onset of the QRS complex. This interval reflects the time required for an electrical impulse to propagate from the myocardial tissue surrounding the sinus node to Purkinje fibers *via* the atrioventricular (AV) node. Consequently, PR interval may be influenced by various factors affecting myocardial fibrosis, ischemia, atrial, or AV node conduction[21]. They examined PR intervals in RA which caused myocardial fibrosis and found no significant difference between patients and controls. This result may be attributed to the fact that AV node function is not affected by chronic inflammatory processes at early stages of RA.

Left atrial diameter is a significant predictor of prognosis, both in the healthy population and in patients with heart disease such as left ventricular dysfunction, mitral regurgitation, or atrial fibrillation. An increased left atrial size is a risk factor for stroke, atrial fibrillation, and sudden death[22]. Arslan et al[11] found a significant increase in left atrial diameter in RA patients compared to the normal population; whereas Birdane et al[12] found no significant difference. The present study found a significant increase in left atrial diameter in RA patients compared to the normal population.

Left ventricular diastolic dysfunction in patients with RA is usually associated with structural abnormalities such as interstitial fibrosis or impaired myocyte relaxation due to ischemia[23]. Left ventricular diastolic dysfunction is assessed using classical Doppler transvalvular flow parameters including E, A, and E/A ratio. Most studies[24-26] have found E/A ratio to be lower in RA patients compared to controls. A result also confirmed in the present study.

Mitral E/e' is one of the parameters in tissue Doppler examination reflecting the longitudinal muscle function of the ventricles. Many studies[9,27] have reported a strong correlation between mitral E/e' ratio and LV filling pressure. An elevated ratio is indicative of diastolic dysfunction. The results of the present study are in line with the literature[11,12] it found a significant increase in mitral E/e' in the RA group compared to the control group.

This study found a significant increase in mitral E/e' and left atrial diameter and a decrease in E/A, which are important indicators of left ventricular diastolic dysfunction. These results suggest that cardiac functions are affected in the long run in RA patients with no cardiac symptoms.

The present study calculated MPI using tissue Doppler echocardiography measurements to assess LV global (systolic + diastolic) function. A significant increase in MPI was noted in the RA group, possibly suggesting impaired left ventricular systolic and diastolic functions. Our finding of impaired MPI in RA patients with no cardiac symptoms may suggest that MPI may have a role in the detection of early cardiac involvement. Çevik et al[13] found no significant difference in MPI between patients with RA and controls. The difference of results between the two studies may be attributed to the use of 1987 ACR criteria[28] in patient selection in the study of Çevik et al[13]. Future studies with a larger number of patients at different clinical stages may provide more clarity as to the role of MPI in the diagnosis, treatment, and prognostic evaluation of patients with RA.

In this study, patients with RA were divided into seropositive and seronegative groups and were compared in terms of PR interval, left atrial diameter, E/A, E/e', and MPI parameters. Left atrial diameter was significantly higher in seronegative patients than that in the seropositive patients. There was no difference in other parameters. Patients with seropositive RA would be normally expected to have higher inflammation, accelerated atherosclerosis due to high inflammation, and a corresponding increase in cardiovascular comorbidity. However, paradoxically, this study found that seronegative RA patients had a higher left atrial diameter than that of the seronegative RA patients, a result that may be attributed to the difference in the number of patients between the two groups.

Analysis of the correlation of disease duration with PR interval, left atrial diameter, E/A, E/e', and MPI parameters found a positive correlation between disease duration and E/e', which is in line with the literature[11,12]. Although disease duration would be expected to be positively correlated with PR interval and left atrial diameter, paradoxically, it was found to have a negative correlation with these values. This result led us to think that some of our patients may have been diagnosed late and their actual duration of illness might be longer than their known duration of illness.

DAS28 had no correlation with PR interval, left atrial diameter, E/A, E/e', or MPI parameters. Likewise, Çukurova et al[29] found no significant difference in DAS28 scores between patients with and without diastolic dysfunction. This suggests that cardiac involvement may progress independently of articular involvement and that regular cardiac examinations may be needed even in patients with mild articular involvement.

Limitations

Coronary angiography is the gold standard to rule out ischemic heart disease. Although patients involved in this study were selected from among those with no cardiac symptoms, some of them may have ischemic heart disease. Fifteen patients were on biological agents. All patients had a history of using DMARDs and corticosteroids. Although these drugs used in the treatment of systemic rheumatic diseases have positive effects on the metabolic and cardiovascular system, they may also have some adverse cardiovascular effects. The medications used by the patients may also have affected cardiac involvement. In addition, the study was conducted with a relatively small number of patients, which is another limitation.

Conclusions

Detecting impaired ventricular diastolic functions in RA may help identify patients at risk of progressive cardiac dysfunction. Early detection of ventricular dysfunction may be useful in clinical practice when predicting prognosis and optimizing treatment. The present study found impaired tissue Doppler measurements and MPI scores in patients compared to controls. Further studies are needed to clarify the utility of tissue Doppler measurements and the MPI in the management of RA.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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The current study received no financial support.

Ethics Approval

The study was approved by the Fırat University Faculty of Medicine Clinical Research Ethics Committee (28.09.2021-90324).

Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Conception and design: Gürkan Akgöl, Arif Gülkesen. Acquisition of data: Mehmet Ali Gelen, Muhammed Fuad Uslu. Analysis and interpretation of data: Gökhan Alkan, Emine Yıldırım Uslu. Drafting the article: Gürkan Akgöl, Emine Yıldırım Uslu. Supervision: Hasan Ata Bolayır. Validation and final approval: all authors.

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