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EVALUATION OF CARDIAC INVOLVEMENT THROUGH TRANSTHORACIC DOPPLER ECHOCARDIOGRAPHY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Aim: Rheumatoid arthritis (RA) is a chronic inflammatory disease found to cause the cardiovascular disease risk. We aimed to evaluate cardiac involvement through transthoracic echocardiography (ECHO) in RA patients and its relationship with age and comorbidities.

Material and Methods: By analyzing the records of follow-up RA patients in outpatient clinics of rheumatology, 200 patients who had ECHO (female/male: 155/45, age range: 57.12±12.08 years, average duration of disease: 108.57±115.99 months) were examined.

Results: The frequency of RF and anti-CCP were 67.2% and 58.4%, respectively, and 40% of patients had other accompanying. According to the ECHO findings, 6% of patients had systolic dysfunction, 4.5% pericardial effusion, 68.1% diastolic dysfunction (DD), 14% valvular disease, and 20.5% pulmonary hypertension. In addition, 81% of patients had an increased left ventricular mass, 33.5% hypertrophy in the left atrium and 11% in the right ventricular area. There was no correlation between seropositivity and ECHO findings, except between anti-CCP and decreased deceleration time (p=0.0013, r=0.214). Left atrial hypertrophy, left ventricular hypertrophy and DD were identified more frequently in patients ages ≥55 years and in patients with accompanying diseases. Pulmonary hypertension was identified more frequently in patients ages ≥55 years.

Conclusion: According to ECHO results, many cardiac involvements, especially DD, were observed in a significant number of RA patients. Factors such as age, autoantibody status, and concomitant diseases may influence the cardiovascular risk. Close monitoring and consideration of cardiovascular interventions can contribute to the prevention of RA-related cardiovascular complications.

Keywords: Rheumatoid arthritis, doppler echocardiography, cardiovascular risk

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that affects many organs including cardiac ones. Several forms of cardiac involvement have been described in RA, and the most common involvement is pericardial effusion and pericarditis (1). In autopsy studies, it was reported a high incidence of involvement of all cardiac structures (myocardial, endocardial and pericardial) in RA patients (2). Myocardial lesions may cause myocardiopathy, conduction defects, structural abnormalities, and cardiac dysfunctions. In RA, the risk of death caused by

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cardiovascular disease was considered to be two-fold higher compared with normal population, which is not explained by traditional cardiovascular risk factors (3,4). The pathological mechanism leading to development of cardiac failure is generally either systolic or diastolic dysfunction or both. It has been demonstrated that diastolic dysfunction is directly related with structural changes in the left ventricle (5). Recent studies have reported the presence of diastolic dysfunction in RA patients which may be clinically silent for years (6-8). It was also confirmed that there is a correlation between left ventricular (LV) diastolic dysfunction and disease duration or the presence of extra-articular manifestations of RA (4).

Easy to use Doppler echocardiography (ECHO) is a non-invasive and sensitive method for detecting systolic and/or diastolic dysfunction and other cardiac abnormalities. However, this conventional method has several limiting factors, such as the effects of changes in preload-afterload and arrhythmia on the method. The purpose of this study was to evaluate the cardiac involvement such as diastolic dysfunction by standard ECHO in patients with RA and compare the findings in terms of age and presence of concomitant disease.

MATERIAL AND METHODS

The study was designed as a retrospective study. Two hundred of 425 patients with RA diagnosed by the revised American College of Rheumatology classification criteria (9) who had ECHO, were recruited from the rheumatology outpatient department. Those who had an ECHO taken at another center were not included, because it was performed by a different echocardiographer and there was missing data. All ECHO was performed in our center, and at that time only one person used it.

Medical records of RA patients were used to extract the data on demographic information, clinical and laboratory findings. The results of ECHO were analyzed with regard to problems with valves, internal chamber size quantification, and systolic and diastolic functions.

ECHO Assessments

Transthoracic M-mode, 2-dimensional and Doppler ECHO was performed with a Toshiba SSA-390A ultrasound machine using a 2.0-3.7 MHz broadband transducer. The left and right ventricles and left atrium measurements were obtained from a parasternal long-axis view in accordance with the American Society of ECHO recommendation. LV mass was calculated using the Penn-convention method and indexed to body surface area. Left ventricular ejection fraction (LVEF) was determined using the modified Simpson's rule in the apical 2- and 4-chamber views. Trans-mitral flow velocity pattern was evaluated from the apical 4-chamber view with pulsed-wave Doppler placing the sample volume at the tips of mitral leaflets during diastole. Early filling deceleration time (DT), atrial (A) and early (E) peak wave velocities, the E/A ratio, and isovolumic relaxation time (IVRT) were measured on three consecutive beats and averaged (10).

Diastolic dysfunction was defined by determination of relaxation abnormality on mitral flow, and it was defined as an E/A ratio <1 or DT >240 ms in patients ages <55 years and an E/A ratio <0.8 and DT >240 ms in patients ages ≥55 years. IVRT measurement, available for all patients, was >90 ms in all patients with abnormal relaxation. According to these definitions, patients were divided into groups with normal or abnormal diastolic function (10).

Statistical Analysis

Statistical analysis was performed by SPSS for Windows 20.0 version. The normal distribution of numerical variables was evaluated with the Kolmogorov-Smirnov test. Besides descriptive statistical methods (median, min-max, mean ± standard deviation), the independent t-test or Mann-Whitney U test were used for continuous variables in comparison of groups. Chi-square test and Fisher's exact test were used for categorical variables. To find the relationships between variables, Spearman correlation analysis was performed. $p<0.05$ was considered sufficient for statistical significance for testing two-sided hypotheses.

RESULTS

By analyzing the records of follow-up patients with RA in the clinics of rheumatology, 200 patients with ECHO (female/male: 155/45, age range: 57.1±12.1 years, average duration of disease: 108.6±116.0 months) were analyzed. It was found that 67.2% of patients had RF positivity, 58.4% had anti-CCP positivity, and 40% (80 patients) of patients had other accompanying diseases (of these comorbidities, 35.5% was hypertension, 5% was ischemic heart disease, and 14.1% was diabetes).

According to the ECHO findings, a significant proportion of RA patients exhibited cardiac involvement; 12 patients (6%) had systolic dysfunction, 9 (4.5%) had pericardial effusion, 128/188 (68.1%) had diastolic dysfunction, 41 (20.5%) had pulmonary hypertension, and 28 (14%) had valvular disease (mitral regurgitation in 17, tricuspid in 15, aortic in 10, and pulmonary only in one patient were identified). There was spontaneous ECHO contrast in two patients with heart valve prostheses. In addition, increased LV mass, left atrium hypertrophy and right ventricular hypertrophy were found in 162 (81%), 67 (33.5%) and 22 (11%) patients, respectively, and there was no correlation between

these parameters and diastolic dysfunction (p>0.05). Moreover, there was no significant correlation between seropositivity and all ECHO findings, except between anti-CCP and decreased DT (r=0.214, p=0.0013). The comparison of demographic findings by age is given in Table 1.

When the ECHO findings were compared by age (58% were above 55 years old) increased LV mass, left atrial hypertrophy, decreased EF, diastolic dysfunction and pulmonary hypertension were identified more frequent in patients ages ≥55 years (Table 1). Although these increased frequencies of ECHO findings in elderly patients, there was no significant difference in terms of presence of accompanying diseases (Table 2). There was significant increase in frequency of diastolic dysfunction, left atrial and LV hypertrophy in patients with accompanying diseases under 55 years old, as it expected. However, the frequency of diastolic dysfunction and LV hypertrophy were 37.3% and 67.2% in patients without accompanying diseases under 55 years old, respectively (Table 3). In addition, there was no significant difference between the two genders, except the frequency of LV hypertrophy in female patients (female: 71%, male: 46.7%; p=0.003).

When we evaluated the correlation between ECHO findings and demographic features, there was significant correlation between

Table 1. The comparison of echocardiographic findings in terms of ages

n (%)	<55 years old (n=84)	≥55 years old (n=116)	p
Age (mean ± std) (min-max; median)	45.8±6.7 (26-54; 47.5)	65.3±7.7 (55-89; 64)	**0.000***
Gender (female)	62 (74.1)	93 (80)	0.288
Disease duration (mean ± std) (min-max; median)	86.1±93.7 (3-476; 42)	124.7±127.6 (4-602; 85)	**0.009***
Concomitant diseases Diabetes mellitus Hypertension Ischemic heart disease	23 (27.4) 6 (7.1) 21 (25) 2 (2.4)	57 (49.1) 22 (19) 50 (43.1) 8 (6.9)	**0.002*** **0.017*** **0.008*** 0.197ξ
Decreased ejection fraction	1 (1.2)	11 (9.6)	**0.015***
Diastolic dysfunction	37/81 (45.7)	91/107 (85.0)	**0.000***
Left atrial hypertrophy	19 (22.4)	48 (41.7)	**0.006***
Right ventricular hypertrophy	6 (7.1)	16 (13.9)	0.138
Left ventricular hypertrophy	62 (57.6)	100 (71.3)	**0.027***
Pulmonary hypertension	8 (9.4)	33 (28.7)	**0.001***
Deceleration time (minute) (mean ± std)	206.4±35.2	229.0±40.5	**0.000***
LVEF (%) (mean ± std)	69.8±6.7	66.0±12.9	**0.052**
LV mass index (g/m^2) (mean ± std)	146.1±44.6	163.4±62.7	**0.031***
Left atrium (cm) (mean ± std)	3.7±0.4	4.0±0.6	**0.000***
Right ventricles (cm) (mean ± std)	2.3±0.3	2.4±0.3	**0.032***
Pulmonary artery pressure (mmHg) (mean ± std)	27.7±7.7	32.6±10.5	**0.006***

Std: Standard deviation,*: p<0.05, ξ: Fisher's exact test was used, LVEF: Left ventricular ejection fraction

Table 2. The effect of presence of concomitant diseases on echocardiographic changes in patients ages ≥55 years

	Concomitant diseases		
n (%)	With (n=57)	Without (n=59)	p
Gender (female)	48 (84.2)	45 (76.3)	0.745
Decreased ejection fraction	7 (12.3)	4 (6.8)	0.312
Diastolic dysfunction	47/53 (88.7)	44/54 (81.5)	0.297
Left atrial hypertrophy	24 (42.1)	24 (40.7)	0.876
Right ventricular hypertrophy	9 (15.8)	7 (11.9)	0.540
left ventricular hypertrophy	49 (85.9)	51 (86.4)	0.941
Pulmonary hypertension	20 (35.1)	13 (22.0)	0.119

Table 3. The effect of presence of concomitant diseases on echocardiographic changes in patients ages <55 years

	Concomitant diseases		
n (%)	With (n=23)	Without (n=61)	p
Gender (female)	19 (82.6)	43 (70.5)	0.260
Decreased ejection fraction	1 (4.3)	0 (0)	0.274
Diastolic dysfunction	15/22 (68.2)	22/59 (37.3)	0.013*
Left atrial hypertrophy	9 (41.3)	10 (16.4)	0.026*
Right ventricular hypertrophy	2 (8.7)	4 (6.6)	0.734
Left ventricular hypertrophy	21 (91.3)	41 (67.2)	0.025*
Pulmonary hypertension	1 (4.3)	7 (11.5)	0.321

*: p<0.05

decreased EF and age (r=0.17, p<0.014), presence of diabetes mellitus (r=0.22, p=0.002) and disease duration time (r=0.26, p=0.000), and between diastolic dysfunction and age (r=0.41, p=0.000), presence of concomitant diseases (r=0.29, p<0.001) and disease duration time (r=0.18, p=0.016).

DISCUSSION

It has been reported increased mortality rate due to cardiovascular events in RA patients, and many of these patients did not experience clinical cardiac symptoms (1,3,5,11,12). This study evaluated the cardiac involvements by standard ECHO such as valvular diseases, diastolic dysfunction and compared the findings in terms of age and presence of concomitant disease in patients with RA. In our study, diastolic dysfunction was detected in 68.1% of all patients, and was found to be significantly higher in patients over 55 years of age (p=0.00). Moreover, 8.5% of patients had valvular dysfunction, 6% had systolic dysfunction, and 4.5% had pericardial effusion. The prevalence of pulmonary hypertension in our study was found to be 20.5%, similar to a previous study (21-27.5%) (13).

Chronic inflammation causes microvascular and endothelial dysfunction, causing myocardial remodeling and fibrosis, and it is thought that LV dysfunction results from this (14). The prevalence of diastolic dysfunction (detected as relaxation abnormalities during LV filling) in the general population has been reported to be 11-34.7%, and increases with age. It has been defined as one of the important causes of heart failure (6,15-17). Diastolic dysfunction has been demonstrated in many studies at a rate of 55-66% in patients with RA without clinical symptoms (3,5,8,18-20). Dal Piaz et al. (20) published a prospective study analyzing the occurrence of diastolic dysfunction in asymptomatic patients with RA followed for one year. Diastolic dysfunction has been found in 26% of RA patients at baseline, and in an additional 24% after one year, for a total of 60% without cardiac symptoms (20). This finding shows how important close monitoring for diastolic dysfunction is in routine practice. Although, it has been reported that LV wall thickening, high LV mass index, and increased left atrial size are associated with diastolic dysfunction (5,7), in the present study we did not find any correlation between diastolic dysfunction and ventricular and atrial hypertrophy. The sample size of the present study was larger than others [in Arslan et al. (7) study' n=52, in Gonzalez-Juanatey el al. (3) study' n=47], and all patients in these studies were ≥55 years old. It is thought that the current difference may be due to this.

In the study, which included 145 RA patients (83% women), the increase in LV muscle mass was found to be significantly higher in women in the follow-up ECHO. They concluded that women with RA had the strongest association with LV hypertrophy, regardless of the presence of CVD risk factors or RA-specific features (21). In the present study, similar to this study, increased LV mass was detected more in female patients in our study (female: 71%, male: 46.7%; p=0.003).

In a study of eighty RA patients under 55, lower ejection fraction and LV diastolic dysfunction have been found to be more common among the anti-CCP positive patients (p=0.01 and p=0.034, respectively) (22). In another study published in 2016, it was noted that inflammation and anti-CCP status in the assessment of cardiovascular mortality in patients with RA may influence the dynamic changes in LV function over time (12). However, in our study, a significant relationship was detected only between anti-CCP seropositivity and the decrease in DT (r=0.214, p=0.0013).

Unlike other studies, in this study, the patients were also compared according to age groups. It is well known that diastolic dysfunction develops with increasing age (12), and in the present study, the increase in LV mass, left atrial hypertrophy, and diastolic dysfunction were detected more frequently in patients aged ≥55 years. However, there were no differences between with and without comorbidities in ECHO findings such as diastolic dysfunction in this patient group. On the other hand, in the presence of comorbidities, there was a significantly increased frequency of diastolic dysfunction, left atrial hypertrophy, and LV mass in patients under 55. This showed that young patients should be closely monitored for cardiovascular complications, especially in the presence of comorbidities.

Study Limitations

This study had some limitations, including small sample size, the lack of a control group and retrospective design. ECHO is not routinely examined for RA patients in the outpatient clinic. Since ECHO is routinely performed on patients hospitalized during disease diagnosis or disease activation, the patients included in the study generally consisted of this group of patients. This can be considered as another limitation.

CONCLUSION

This study highlights the complexity of cardiac involvement in RA patients and the need for meticulous cardiovascular monitoring, irrespective of autoantibody status. The influence of age, along with the presence of comorbid conditions, underscores the necessity for a holistic approach to the care of RA patients. Considering these multifactorial aspects, timely interventions are essential for mitigating the risk of RA-associated cardiovascular complications. Detecting diastolic dysfunction may help reduce cardiovascular mortality in patients with RA without clinical symptoms.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., F.T.K., T.Ş., B.Y., F.C., D.T.K., A.C., Concept: A.Y., T.Ş., Design: A.Y., T.Ş., Data Collection or Processing: A.Y., T.Ş., B.Y., F.C., Analysis or Interpretation: A.Y., Literature Search: A.Y., F.T.K., Writing: A.Y., F.T.K., D.T.K., A.C.

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