Epicardial fat thickness in patients with rheumatoid arthritis

Erdem Fatma[2], Koç Bünyamin[1], Sarikaya Savas[3], Uçar Mehmet[4], Yazıcı Selma[2], Boyraz Ismail[1], Caglar Sabri[1], Ozyalvacli Gulzade[5], Dönmez Ibrahim[1], Yazici Mehmet[1]

1. Department of Cardiology, Abant Izzet Baysal University School of Medicine, Bolu, Turkey
2. Department of Cardiology, Bozok University School of Medicine Yozgat, Turkey
3. Department of Physical Medicine and Rehabilitation, Abant Izzet Baysal University School of Medicine, Bolu, Turkey
4. Department of Physical Medicine and Rehabilitation, Bozok University School of Medicine Yozgat, Turkey
5. Department of Pathology, Abant Izzet Baysal University School of Medicine, Bolu, Turkey

Abstract

Background: Epidemiologic data indicates that rheumatoid arthritis is an independent risk factor for cardiovascular disease. Epicardial adipose tissue is a novel cardio-metabolic risk factor. Our aim was to evaluate epicardial fat thickness (EFT) using echocardiography in patients with rheumatoid arthritis compared to healthy control subjects. Secondly, we investigated relationship between epicardial fat thickness and clinical and echocardiographic parameters in patients with rheumatoid arthritis.

Method: The study population included 76 consecutive patients with rheumatoid arthritis (64 female; mean age, 53 ±11 years, median disease duration, 7.8 years) and 50 healthy subjects as controls (39 female; mean age, 52 ± 6 years). All patients underwent echocardiography to assess left ventricular diastolic dysfunction, left ventricular hypertrophy and EFT. All values were compared between groups.

Results: EFT was higher in rheumatoid arthritis patients than in healthy controls (0.66±0.20 vs. 0.54±0.18; p= 0.003). Thickness of Intra Ventricular Septum (IVS) (1.1±0.06 and 9.8±0.08; p=0.001) and posterior wall (PW) (0.98±0.05 and 0.93±0.08; p=0.015) was higher in patients with rheumatoid arthritis compared to healthy controls. Early diastolic myocardiac peak velocity or late diastolic mitral peak velocity (E/A) ratio was lower in rheumatoid arthritis patients compared to healthy patients (1.1 ±0.8 and 1.24±0.1 p=0.001) as well as, E/e' was higher in Rheumatoid arthritis (RA) patients than healthy patients. (E/e':8.7±1.6 and 8.0±1.4 p=0.020). In patients with rheumatoid arthritis, EFT was positively correlated with hypertension and duration of disease and E/e' (r: 0.10, p: 0.010, r: 0.306, p: 0.004 and r: 0.465 p: 0.007 respectively) and EFT was negatively correlated with E/A (r: -.262 p:0.022)

Conclusion: To our knowledge, this is the first report about epicardial adipose tissue in rheumatoid arthritis patients. Epicardial fat thickness as an indicator of cardiovascular involvement was higher in rheumatoid arthritis patients.

Keywords: Rheumatoid arthritis, epicardial fat thickness, cardiac involvement

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic symmetric and erosive synovitis that preferentially affects peripheral joints, with prevalence of 0.5– 1% in the population[1]. Epidemiologic data indicates that RA is an independent risk factor for cardiovascular disease (CVD)[2,3]. Emerging epidemiological evidence showed that CVDs account for approximately 50% of all RA associated deaths[4].

Epicardial adipose tissue (EAT), a type of visceral adipose tissue, is considered to play a pivotal role in the pathogenesis of coronary artery disease (CAD). Recently, several studies have demonstrated that epicardial fat is associated with insulin resistance[5], increased cardio-metabolic risk[6], inflammatory markers[7,8] and coronary artery disease[9,10]. The echocardiographic measurement of EAT, is an objective, noninvasive, readily available, and less expensive measure than magnetic resonance imaging or computed tomography.

Corresponding author:
Erdem Fatma,
Abant Izzet Baysal University
School of Medicine,
Department of Cardiology,
14280 Bolu, TURKEY
Telephone: +90 374 253 46 16
Fax: +90 374 253 45 59
E-mail:mobitztip1@gmail.com

Our aim was to evaluate epicardial fat thickness (EFT) using echocardiography in patients with rheumatoid arthritis compared to healthy control subjects. Secondly, we investigated the relationship between EFT and clinical and echocardiographic parameters in patients with rheumatoid arthritis.

Methods

Study Population

The study population included 76 consecutive patients with rheumatoid arthritis (64 female; mean age, 53 ±11 years, and median disease duration, 7.8 years) and 50 healthy subjects as controls (39 female; mean age, 52± 6 years). All patients met the American College of Rheumatology's grading criteria for a diagnosis of RA[11]. A detailed history and analysis of patients was performed. The inclusion criteria for the study groups were: age ≥18 years, patient's informed consent, absence of any acute disease. Patients with any of the following features were excluded from participation: patients with valvular heart disease; chronic obstructive pulmonary disease, any other significant systemic disease, obstructive coronary artery disease, history of heart failure, hepatic failure, hypertension, serum creatinine >1.4 mg/dL, patients with a history of diabetes mellitus (or fasting blood glucose >125 mg/dL), pregnant women, patients with hypo or hyperthyroidism, patients with a BMI >25 kg/m2, and patients who wished to consume alcohol during the study period. Also, we excluded patients with : heart failure, significant valvular heart disease, pacemaker implantation, atrial flutter or fibrillation, frequent ventricular pre-excitation and atrioventricular conduction abnormalities, renal failure, previous myocardial infarction, or cerebrovascular accident and poor echocardiographic imaging.

This study was conducted in accordance with the Declaration of Helsinki and was approved by our local ethics committee. Informed consent for the procedure was obtained from each patient.

Echocardiography

All patients underwent echocardiography. Following a resting period of 15 min, all the patients underwent two-dimensional and Doppler echocardiographic evaluation, including tissue Doppler imaging (TDI) with the echocardiogram device using a 3.5-MHz transducer. Echocardiograms of all patients were recorded as standard parasternal and apical images with the patients lying in the left lateral position. The measurement and recordings were carried out as normal inspiratory and end-expiratory. Doppler records of M-mode, pulse and continuous waves were obtained for each case. All the measurements were performed based on the standards of the American Society of Echocardiography by the same cardiologist. Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), ejection fraction (EF), intraventricular septum thickness (IVS), posterior wall thickness (PW) values were defined from the recordings obtained with the conventional echocardiography. In the pulsed-wave echocardiographic transmittal flow screenings, early diastolic mitral peak velocity (E), late diastolic mitral peak velocity (A), were measured based on the reference images of the apical 4 chamber. On TDI, early diastolic myocardial peak velocity (é) was recorded with apical 4-chamber images using a sampling volume of 5 mm in the septal and lateral mitral annular regions. All Doppler measurements were carried out manually E/A, and E/é.

Epicardial fat thickness was evaluated on the free wall of the right ventricle from the parasternal long-axis view, using the aortic annulus as an anatomic reference. Epicardial fat thickness, identified as an echo-free space between the myocardium and visceral pericardium on two-dimensional echocardiography, was measured perpendicularly, ahead of the right ventricular free wall, at the end of diastole, for three cardiac cycles[12].

Laboratory

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least eight hours. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined using standard methods.

Statistical analysis

The statistical analyis was performed using software (SPSS 18.0). Parametric values were given as mean ± standard deviation and non-parametric values were given as a percentage. To compare parametric continuous variables, the Student's t-test was used; to compare nonparametric continuous variables, the Mann–Whitney U-test was used. Categorical data was compared by the Chi-square distribution. Correlation analysis was performed to determine the relationship between epicardial fat tissue and other cardio-metabolic risk factor. Two-tailed P-values of less than 0.05 were considered to indicate statistical significance.

Results

Clinical Features

According to the basic clinical and demographic characteristics, both groups of the study were similar with regard to age, body mass index, fasting glucose, hypertension, diabetes mellitus, and smoking status (table 1).

Table 1: Basal characteristic of patients

	Rheumatoid arthritis (n=76)	Healthy controls (n=50)	P value
Age	53 ± 11	52 ± 6	0.430
Gender (Female)	64 84%	39 78%	0.257
Diabetes mellitus, %	8 10%	6 11%	0.105
Hypertension, %	35 47%	21 43%	0.401
Smoking, %	7 9.2%	6 12.2%	0.416
Rheumatoid factor	23.7 (1.0-200)	-	
Disease duration, years	7.84 (2.4-30)	-	
Steroid use, n	29 (38%)	-	
C-reactive protein, mg/dl	19.2 ± 46.3	1.7 ± 3.7	0.007
Body mass Index	32 ± 6	34 ± 8	0.122
Waist circumstance	101.12±13.62	103.18±14.53	0.424
Glucose, mg/dl	93.18±16.83	98.7333±13.26	0.770
Triglyceride, mg/dl	137.75±52.29	149.41±60.99	0.360
High density lipoprotein, mg/dl	42.87±6.98	41.81±7.0	0.494
Total cholesterol, mg/dl	203.70±53.70	211.31±47.38	0.529
Low density lipoprotein, mg/dl	126.62±34.28	122.16±33.384	0.553

Echocardiographic data

Comparison of the baseline echocardiographic values among rheumatoid arthritis patients and healthy controls are shown in table 2. Thickness of IVS (1.1±0.06 and 9.8±0.08; p=0.001) and PW (0.98±0.05 and 0.93±0.08; p=0.015) were higher in patients with rheumatoid arthritis compared to healthy controls.

Table 2: Echocardiographic features of patients

	Rheumatoid arthritis (n=76)	Healthy controls (n=50)	P value
Epicardial fat thickness,cm	0.66 ± 0.20	0.54 ± 0.18	**0.003**
Ejection fraction, %	63 ± 6	62 ± 4	0.733
LVEDD,cm	4.5±0.31	4.4±0.27	0.536
LAD,cm	3.43±0.42	3.46±0.52	0.647
IVS,cm	1.1±0.06	0.98±0.08	**0.010**
PW, cm	0.98±0.05	0.93±0.08	**0.015**
Diastolic function			
E cm/s	74±10	86±12	**0.001**
A cm/s	76±14	73±9	**0.140**
E/A	1.1±0.8	1.24±0.1	**0.001**
e' cm/s	8.6±1.5	11±1.6	**0.001**
E/e'	8.7 ±1.6	8.0 ± 1.4	**0.020**

E wave and E/A ratio was lower in rheumatoid arthritis patients compared to healthy patients (E: 74±10 and 86±12 p=0.01 vs E/A: 1.1 ±0.8 and 1.24±0.1 p=0.001) as well as, E/e' was higher in RA patients than non-rheumatoid arthritis patients. (E/e':8.7±1.6 and 8.0±1.4 p=0.020). EFT was higher in rheumatoid arthritis patients compared to healthy controls (0.66±0.20 vs. 0.54±0.18; p:0.003). In patients with rheumatoid arthritis, EFT was positively correlated with hypertension and duration of disease and E/e' (r: 0.10 p:0.010, r:0.306 p: 0.004 and r:0.465 p: 0.007 respectively) (Figure 1) and EFT was negatively correlated with e/a (r: -.262 p:0.022 and) (Figure 2).

Figure 1

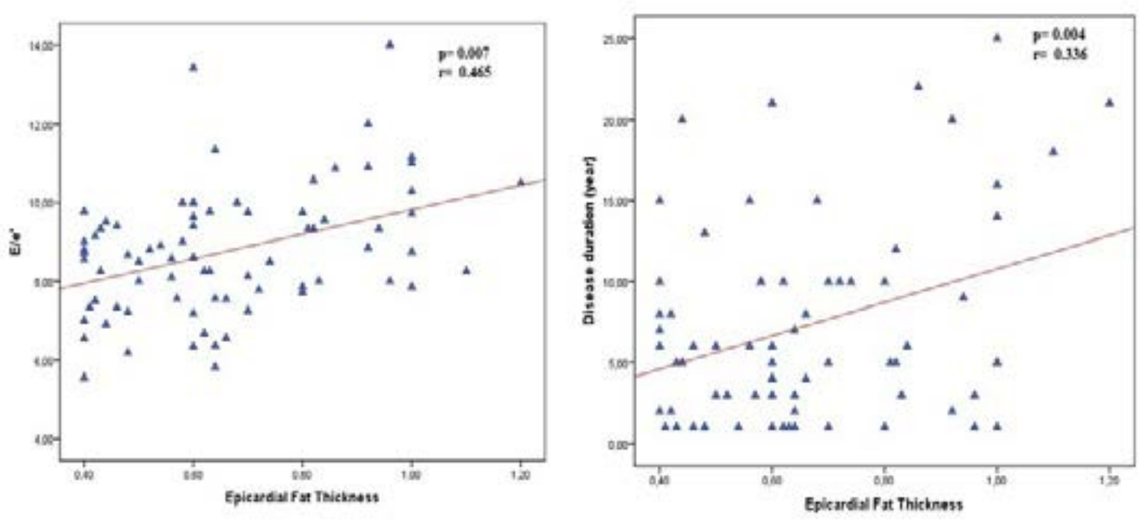
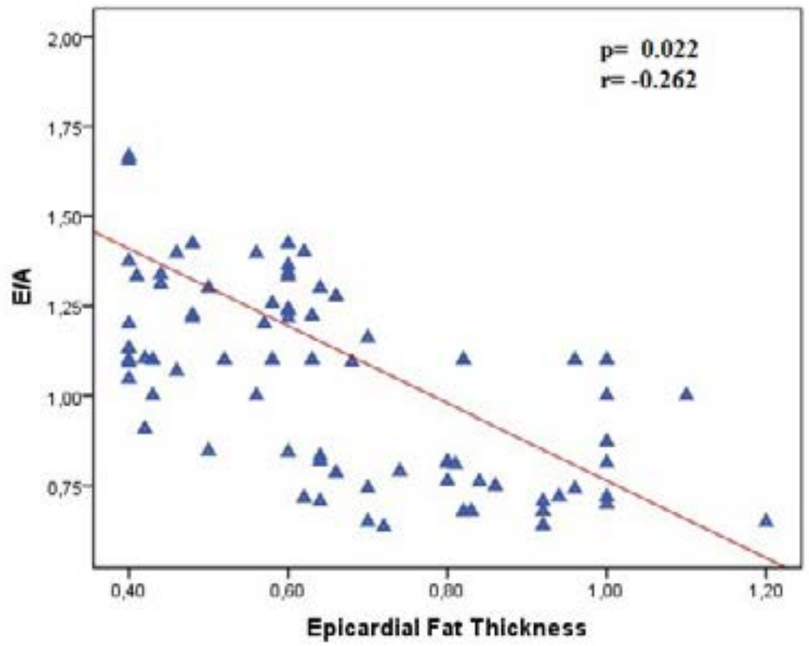


Figure 2



Left ventricular diastolic dysfunction was detected in 30 (39%) of 75 patients with rheumatoid arthritis; 24 patients presented with diastolic dysfunction I and 6 patients presented with diastolic dysfunction II.

Discussion

In our study, we showed that EFT was higher in patients with rheumatoid arthritis than in the healthy control. Secondly, we demonstrated that left ventricular wall thickness and diastolic dysfunction were higher and EFT was well correlated with diastolic dysfunction and disease duration in patients with rheumatoid arthritis. These findings may be associated with cardiovascular involvement in patients with rheumatoid arthritis.

Rheumatoid arthritis is linked with an increase in mortality because of stimulation of coronary and cerebrovascular atherosclerosis.[13] Emerging epidemiological evidence showed that CVDs account for approximately 50% of all RA associated deaths[4]. EAT, a type of visceral adipose tissue, is thought to play a pivotal role in the pathogenesis of coronary artery disease (CAD). EAT releases a wide range of biologically active molecules that modulate vascular smooth-muscle contraction. Their paracrine effects might be attributable to their location being close to the adventitia and extravascular bed[14-16] Gastaldelli et al.[16] reported the existence of a link between EAT and hypertension, atherosclerosis, and coronary heart disease. Nakanishi and colleagues[17] reported that increased epicardial fat volume measured by CT is associated with greater progression of coronary artery calcification. Transthoracic echocardiography provides non-invasive assessment of EFT[6, 12]. Several studies have emphasized the link between EFT and the severity of coronary artery disease (CAD)[19-21]. EFT has an important role in the inflammatory process within the atherosclerotic plaque[9]. In our study, we demonstrated that EFT was higher in patients with rheumatoid arthritis. In addition , we showed that EFT was associated with duration of disease, hypertension, and diastolic dysfunction in patients with rheumatoid arthritis. These findings indicate that rheumatoid arthritis patients may be having an underlying risk of cardiovascular disease.

Isolated diastolic dysfunction is related to prominent increase in all-cause mortality in the general population[22,23]. Left ventricular diastolic dysfunction (LVDD) is frequently related to common structural abnormalities, such as hypertrophy or interstitial fibrosis, and impaired myocyte relaxation due to ischemia[24]. Previous studies showed the existence of LVDD in patients with RA without clinically prominent cardiac disease.[25-27]. Liang et al. investigated the prevalence of LVDD in patients with RA. They found that patients with RA have a higher prevalence of LVDD than those healthy controls and RA duration is also independently associated with LVDD[28]. In our study, LVDD was detected in 30 (39%) of 75 patients with rheumatoid arthritis; 24 patients presented with diastolic dysfunction I and 6 patients presented with diastolic dysfunction II. Rudominer et al. showed that left ventricular hypertrophy is higher compared to healthy patients[3]. LV hypertrophy predicts cardiovascular outcomes independent of traditional risk factors[30-32]. In our study, we found that left ventricular wall thickness was increased in patients with rheumatoid arthritis.

The use of the Doppler echocardiography technique to evaluate left ventricular filling by trans-mitral flow is considered a reliable method.[2] The relation between trans-mitral flow variation and disease duration in rheumatoid arthritis indicate a subclinical myocardial involvement.[25] In our study, we showed that diastolic function in patients with rheumatoid arthritis was impaired compared to those healthy patients. In addition, we demonstrated that disease duration in patients with rheumatoid arthritis was associated with diastolic dysfunction: consistent with previous studies.

Limitations

Some limitations of this study are evident. The primary limitation of our study was the small sample size. A small sample size has low statistical power and, thus, may yield false-negative results. The other limitation of our study is its cross-sectional design. The results cannot be generalized to the general population. Neither can we apply our results to the general population due to the numerous exclusion criteria. Despite this, we believe that our findings provide a valuable contribution to the EFT and RA. Future prospective much larger multicenter studies are required to confirm our results.

Conclusion

Epicardial fat thickness as an indicator of cardiovascular involvement was higher in patients with rheumatoid arthritis. Also, we showed that diastolic dysfunction and left ventricular hypertrophy were higher in rheumatoid arthritis patients. These findings suggest that subclinical cardiac involvement in patients with RA and those patients may be underlying risk factors for development of cardiovascular disease.

Conflict of Interest: None

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