Evaluation of atrial electromechanical delay and left atrial mechanical functions in patients with rheumatoid arthritis

Romatoit artritli hastalarda atriyal elektromekanik gecikme ve sol atriyum mekanik fonksiyonlarının değerlendirilmesi

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Objectives: The aim of this study was to evaluate atrial electromechanical delay measured by tissue Doppler imaging (TDI) and left atrial (LA) mechanical functions in patients with rheumatoid arthritis (RA).

Study design: The study included 68 patients (53 females, 15 males; mean age 43.7 years) with RA. Using TDI, atrial electromechanical coupling (PA) was measured from the lateral mitral annulus (PA lateral), septal mitral annulus (PA septum), and right ventricular tricuspid annulus (PA tricuspid). Left atrial volumes (maximal, minimal, and pre-systolic) were measured by the method of discs in the apical four-chamber view and were indexed to body surface area. Mechanical function parameters of the LA were calculated. The results were compared with those of 41 age- and gender-matched healthy volunteers (32 females, 9 males; mean age 41.9 years).

Results: Patients with RA had significantly prolonged PA lateral, PA septum, and intra- (PA septum-PA tricuspid) and interatrial (PA lateral-PA tricuspid) electromechanical delays compared to controls (p<0.0001, p=0.05, p<0.0001, and p<0.0001, respectively). Left atrial volumes were similar in the two groups (p>0.05). Left atrial passive emptying fraction was significantly decreased, LA active emptying volume and active emptying fraction were increased in RA patients (p=0.05, p=0.01, and p<0.0001; respectively). Interatrial electromechanical delay was correlated with systolic blood pressure (r=0.20, p=0.04), left ventricular mass index (r=0.22, p=0.02), C-reactive protein (CRP) (r=0.27, p=0.005), and LA active emptying fraction (r=0.29, p=0.002). In linear regression analysis, LA active emptying fraction and CRP were independent variables of interatrial electromechanical delay (β=0.28, p=0.002 and β=0.25, p=0.006, respectively).

Conclusion: Prolonged electromechanical delays and impaired LA mechanical functions may be an early manifestation of subclinical cardiac involvement in RA patients.

Key words: Arthritis, rheumatoid/complications; echocardiography, Doppler; heart atria; heart conduction system; ventricular dysfunction, left/etiology.

Amaç: Bu çalışmada, romatoit artritli (RA) hastalarda doku Doppler görüntüleme (DDG) ile ölçülen atriyal elektromekanik gecikme süresi ve sol atriyum (SA) mekanik fonksiyonları değerlendirildi.

Çalışma planı: Çalışmaya RA'lı 68 ardışık hasta (53 kadın, 15 erkek; ort. yaş 43.7) alındı. Atriyal elektromekanik süre (PA) DDG ile lateral mitral halka (PA lateral), septal mitral halka (PA septum) ve sağ ventrikül triküspit halkadan (PA triküspit) ölçüldü. Sol atriyum hacimleri (maksimum, minimum ve sistol öncesi) apikal dört boşluktan disk yöntemi ile ölçüldü ve vücut yüzey alanına oranlandı. Sol atriyum mekanik fonksiyonları hesaplandı. Sonuçlar, yaş ve cinsiyet uyumlu, sağlıklı 41 gönüllüden (32 kadın, 9 erkek; ort. yaş 41.9) oluşturulan kontrol grubuyla karşılaştırıldı.

Bulgular: Kontrol grubuyla karşılaştırıldığında, RA'lı hastalarda PA lateral, PA septum ve intra-atriyal (PA septum-PA triküspit) ve interatriyal (PA lateral-PA triküspit) elektromekanik gecikme süreleri anlamlı derecede uzamış idi (sırasıyla, p<0.0001, p=0.05, p<0.0001 ve p<0.0001). Sol atriyum hacimleri iki grupta benzer bulundu (p>0.05). Hasta grubunda SA pasif boşalma oranı azalmış, aktif boşalma hacmi ve aktif boşalma oranı artmış idi (sırasıyla, p=0.05, p=0.01 ve p<0.0001). İnteratriyal elektromekanik gecikme süresi, sistolik kan basıncı (r=0.20, p=0.04), sol ventrikül kütle indeksi (r=0.22, p=0.02), serum C-reaktif protein (CRP) düzeyi (r=0.27, p=0.005) ve SA aktif boşalma oranı (r=0.29, p=0.002) ile ilişkili bulundu. Çoklu lineer regresyon analizinde, SA aktif boşalma oranı ve CRP, interatriyal elektromekanik gecikme süresi ile bağımsız ilişki gösterdi (sırasıyla, β=0.28, p=0.002 and β=0.25, p=0.006).

Sonuç: Uzamış elektromekanik gecikme süreleri ve SA mekanik fonksiyonlarındaki bozukluklar RA'lı hastalarda subklinik kardiyak tutulumun erken bulguları olabilir.

Anahtar sözcükler: Artrit, romatoit/komplikasyon; ekokardiyografi, Doppler; kalp atriyumu; kalp iletim sistemi; ventrikül disfonksiyonu, sol/etyoloji.

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Rheumatoid arthritis (RA) is a chronic multisystemic and inflammatory disease. The frequency of cardiovascular disease is increased in RA patients, including ischemic heart disease, systolic and/or diastolic heart failure, pericarditis, myocarditis, vasculitis, conduction system abnormalities, and arrhythmias.[1-3] Moreover, although cardiac involvement is often clinically silent, cardiovascular mortality is higher in RA patients.[4]

There are several studies showing that left ventricular (LV) diastolic function may be impaired in RA.[5,6] Additionally, it is well-established that left atrial (LA) mechanical functions play a significant role in maintaining LV stroke volume in patients with impaired LV diastolic function.[7]

There are several studies suggesting that the frequency of atrial and ventricular arrhythmias may be higher in RA patients.[2,8,9] Atrial fibrillation (AF) is the most common type of tachyarrhythmia encountered in clinical practice and is associated with increased morbidity and mortality.[10] Systemic inflammation plays a significant role in AF pathogenesis.[11] The prolongation of intra- and interatrial electromechanical delay and the inhomogeneous propagation of sinus impulses are well-known electrophysiological characteristics of the atria prone to fibrillation. This issue has been evaluated noninvasively by several alternative techniques such as P-wave dispersion and tissue Doppler imaging (TDI) echocardiography.[8,9,12,13]

To our knowledge, atrial conduction times measured by TDI and LA mechanical functions have not been assessed in RA patients. The purpose of this study was to evaluate atrial electromechanical coupling and LA mechanical functions, and to investigate whether atrial electromechanical delay was related to LA mechanical functions in patients with RA.

PATIENTS AND METHODS

Study population. The study included 68 consecutive patients (53 females, 15 males; mean age 43.7±12.1 years) who were diagnosed as having RA according to the revised classification of the American College of Rheumatology.[14] The control group was comprised of 41 age- and gender-matched healthy volunteers (32 females, 9 males; mean age 41.9±10.9 years) selected among medical students or office staff in our hospital.

Exclusion criteria were the presence of the following: coronary artery disease, arterial hypertension, LV wall motion abnormality, LV ejection fraction (EF) less than 50%, primary cardiomyopathy, valvular heart disease, bundle branch block and atrioventricular conduction abnormalities on the electrocardiogram, thyroid dysfunction, anemia, hypercholesterolemia, electrolyte imbalance, renal failure, pulmonary disease, and poor echocardiographic imaging. All the patients were in sinus rhythm and none of them were taking medications such as anti-tumor necrosis factor drugs, antiarrhythmics, tricyclic antidepressants, antihistaminics, and antipsychotics. All the patients were receiving one or more disease-modifying antirheumatic drugs (hydroxychloroquine, methotrexate, and sulfasalazine) and steroids. Erythrocyte sedimentation rate (ESR), levels of C-reactive protein (CRP, mg/dl) and rheumatoid factor (IU/ml), and Disease Activity Score 28 (DAS-28)[15] were obtained from medical records. Written informed consent was obtained from each subject and the institutional ethics committee approved the study protocol.

Conventional echocardiographic examination. Two-dimensional, M-mode, pulsed and color flow Doppler echocardiographic examinations (Vivid 7 Pro, GE, Horten, Norway) with a 2-4 MHz phased array transducer were performed by a cardiologist who was blind to the clinical details and findings of other examinations of each patient and control. During echocardiography, continuous one-lead electrocardiographic recording was obtained. M-mode measurements and conventional Doppler echocardiographic examinations were performed according to the guidelines of the American Society of Echocardiography.[16] All measurements were recorded as average of three cardiac cycles. Left atrium dimension, LV end-systolic and end-diastolic dimensions, diastolic ventricular septal thickness, and diastolic LV posterior wall thickness were measured in the parasternal long-axis view. Left ventricular EF was estimated using the Simpson's rule. Left ventricular mass was calculated with the Devereux equation[17] and was indexed to body surface area (BSA).

Atrial electromechanical coupling. Tissue Doppler echocardiography was performed with a transducer frequency of 3.5 to 4.0 MHz, adjusting the spectral pulsed Doppler signal filters to obtain the Nyquist limit of 15 to 20 cm/sec, and using the minimal optimal gain setting. The monitor sweep speed was set at 50 to 100 mm/sec to optimize the spectral display of myocardial velocities. In apical four-chamber view, the pulsed Doppler sample volume was placed at the level of the LV lateral mitral annulus, and subsequently at the septal mitral annulus and right

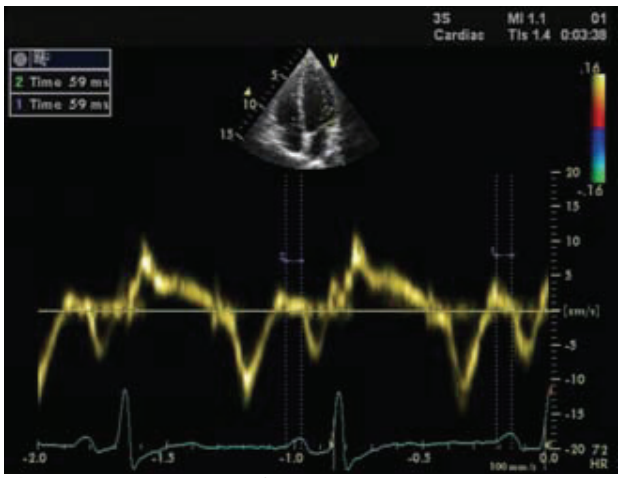

Figure 1. Measurement of the PA interval with tissue Doppler imaging, which denotes time interval from the onset of P wave on the surface electrocardiogram to the beginning of the late diastolic wave (A_m wave).

ventricular tricuspid annulus. The sampling window was positioned as parallel as possible with the myocardial segment of interest to obtain the optimal angle of imaging. Atrial electromechanical coupling was defined as the time interval from the onset of P wave on the surface electrocardiogram to the beginning of the late diastolic wave (A_m wave), i.e. PA interval (Fig. 1), and was measured from the lateral mitral annulus (PA lateral), septal mitral annulus (PA septum), and right ventricular tricuspid annulus (PA tricuspid).[18] All PA intervals were averaged over three consecutive beats. The difference between the lateral and tricuspid PA intervals was defined as interatrial electromechanical delay, and the difference between the septal and tricuspid PA intervals was defined as intra-atrial electromechanical delay.[18]

Assessment of left atrial mechanical functions. Left atrial volumes were measured by the method of discs in the apical four-chamber view at end-systole (maximal, V_{max}), end-diastole (minimal, V_{min}) and at the onset of atrial systole (P wave on electrocardiogram, V_p) (Fig. 2). All volumes were indexed to BSA and expressed in ml/m^2. Then, the following LA emptying function parameters were calculated: LA passive emptying volume = $V_{max} - V_p$; LA passive emptying fraction = $(V_{max} - V_p)/V_{max}$; LA active emptying volume = $V_p - V_{min}$; LA active emptying fraction = $(V_p - V_{min})/V_p$; conduit volume = [LV stroke volume - $(V_{max} - V_{min})$]; and LA total emptying volume = $V_{max} - V_{min}$.[19]

Reproducibility. Intraobserver variability was assessed in 20 subjects selected randomly from the patient group by repeating the measurements under the same basal conditions. To test the interobserver variability, the measurements were performed offline from video recordings by a second observer. Reproducibility of atrial electromechanical coupling obtained by TDI was assessed by coefficient of variation (CV) between measurements.

Intraobserver variability was 5.7% for PA lateral, 6.8% for PA septum, and 5.8% for PA tricuspid, respectively. Interobserver variability was 5.0% for PA lateral, 7.3% for PA septum, and 5.5% for PA tricuspid, respectively.

Statistical analysis. All analyses were made using the SPSS (SPSS for Windows 9.0) software package. Continuous variables were expressed as mean ± standard deviation; categorical variables were expressed as percentages. Categorical data were compared with the chi-square test. Pearson's correlation coefficients were used to assess the strength of relationship between continuous variables. A stepwise, multiple regression analysis was used to identify significant determinants of interatrial electromechanical delay, which included variables that correlated with a p value of less than 0.1 in the Pearson's correlation analysis. A p value of less than 0.05 was considered significant.

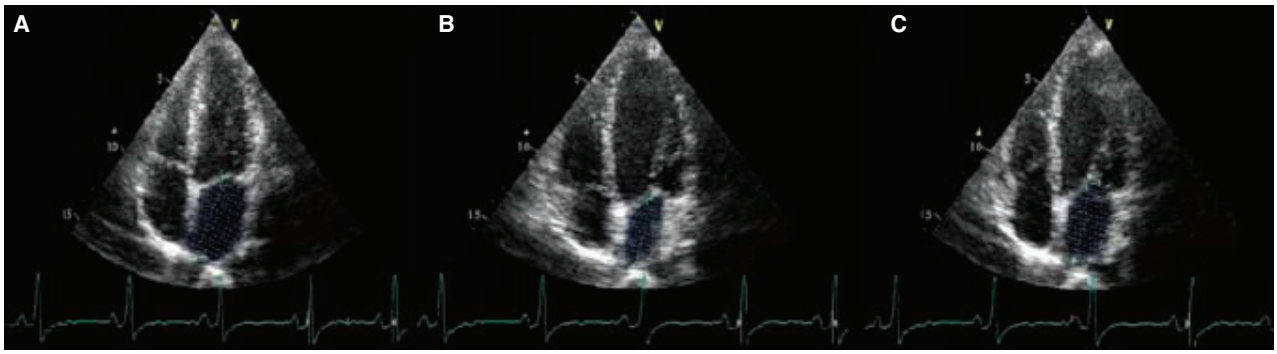

Figure 2. Left atrial (LA) volumes measured in the apical four-chamber view by means of two-dimensional echocardiography. **(A)** LA maximum volume at end-systole (35 ml), **(B)** LA minimum volume at end-diastole (8 ml). **(C)** LA volume before atrial systole, the beginning of the P wave on the electrocardiogram (17 ml).

Table 1. Clinical characteristics, laboratory and echocardiographic findings of the two groups

	Patients with RA (n=68)			Control group (n=41)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			43.7±12.1			41.9±10.9	N.S
Sex							N.S
Male	15	22.1		9	22.0		
Female	53	77.9		32	78.1		
Body mass index (kg/m^2)			27.8±4.5			27.6±5.0	N.S
Body surface area (m^2)			1.8±0.2			1.8±0.1	N.S
Smoking	14	20.6		8	19.5		N.S
Systolic blood pressure (mmHg)			117.4±11.1			115.4±9.8	N.S
Diastolic blood pressure (mmHg)			75.5±7.2			73.6±7.1	N.S
Heart rate (beats/min)			82.2±10.8			78.6±11.4	N.S
Left ventricular							
End-diastolic dimension (mm)			46.8±3.6			46.8±4.0	N.S
End-systolic dimension (mm)			29.3±3.3			29.4±3.4	N.S
Ejection fraction (%)			66.4±9.6			67.0±5.9	N.S
Mass index (g/m^2)			103.4±23.3			99.5±16.8	N.S
Septum thickness (mm)			10.1±1.0			9.7±1.1	N.S
Posterior wall thickness (mm)			8.9±0.8			8.6±1.2	N.S
Left atrium dimension (mm)			33.4±3.9			33.5±4.8	N.S
Erythrocyte sedimentation rate (mm/hr)			32.4±19.5			16.9±12.3	**<0.0001**
C-reactive protein (mg/l)			8.7±12.8			4.1±2.5	**0.025**
Rheumatoid factor (IU/ml)			171.2±210.5			9.8±4.9	**<0.0001**
Disease Activity Score 28			4.7±1.0			–	
Disease duration (months)			71.1±66.7			–	

RA: Rheumatoid arthritis; NS: Not significant.

RESULTS

Clinical characteristics and echocardiographic findings of the two groups are shown in Table 1. Age, sex, body mass index, BSA, smoking status, systolic and diastolic blood pressure, heart rate, LV end-diastolic dimension, LV end-systolic dimension, LV mass, LA dimension, and LV EF were similar between the two groups (p>0.05). However, patients with RA exhibited significantly higher levels of ESR (p<0.0001), serum CRP (p=0.025), and RF (p<0.0001). The mean DAS-28 score was 4.7±1.0 in RA patients and the mean disease duration was 71.1±66.7 months (Table 1).

Atrial electromechanical coupling. The atrial electromechanical coupling intervals measured from different sites by TDI are shown in Table 2. Patients with RA had significantly prolonged PA lateral, PA septum, and intra- and interatrial electromechanical delays compared with healthy controls (p<0.0001, p=0.05, p<0.0001, and p<0.0001, respectively).

Left atrial mechanical functions. Left atrial volume measurements are presented in Table 3. The two groups were similar with respect to maximum LA volume, V_p, V_{min}, LA passive emptying volume, and LA total emptying volume (p>0.05). However, LA passive emptying fraction was significantly decreased, LA active emptying volume and LA active emptying fraction were significantly increased in RA patients (p=0.05, p=0.01 and p<0.0001, respectively).

Interatrial electromechanical delay was not correlated with age, diastolic blood pressure, LV EF,

Table 2. Findings of atrial electromechanical coupling measured by tissue Doppler imaging

	Patients with RA (n=68)	Control group (n=41)	
	Mean±SD	Mean±SD	*p*
PA lateral (msec)	61.0±8.3	52.0±6.7	<0.0001
PA septum (msec)	42.7±6.9	40.1±6.0	0.05
PA tricuspid (msec)	37.0±4.7	37.9±5.0	N S
PA lateral - PA tricuspid (msec)*	24.0±7.3	14.0±3.8	<0.0001
PA septum - PA tricuspid (msec)**	5.7±5.6	2.2±2.2	<0.0001

RA: Rheumatoid arthritis; NS: Not significant; PA: The interval with tissue Doppler imaging, from the onset of P wave on the surface electrocardiogram to the beginning of the late diastolic wave (A_m wave). *Interatrial and **intra-atrial electromechanical delays.

Table 3. Left atrial volume measurements

	Patients with RA (n=68)	Control group (n=41)	
	Mean±SD	Mean±SD	*p*
Maximum volume at end-systole (ml/m^2)	25.4±7.5	25.0±6.1	N.S
Volume at the beginning of atrial systole (ml/m^2)	16.3±5.2	15.2±4.7	N.S
Minimal volume at end-diastole (ml/m^2)	8.7±3.1	8.7±2.6	N.S
Passive emptying volume (ml/m^2)	9.1±4.4	9.8±3.8	N S
Passive emptying fraction (%)	34.8±11.4	39.4±12.0	**0.05**
Conduit volume (ml/m^2)	20.5±6.7	22.1±6.7	N S
Active emptying volume (ml/m^2)	8.0±3.0	6.5±3.1	**0.01**
Active emptying fraction (%)	47.9±9.0	40.8±11.4	**<0.0001**
Total emptying volume (ml/m^2)	17.1±5.4	16.3±4.8	N S

NS: Not significant.

LA diameter, LA volume index, RA diameter, RA volume index, disease duration, and DAS-28. It was mildly and significantly correlated with systolic blood pressure (r=0.20, p=0.04), LV mass index (r=0.22, p=0.02), CRP (r=0.27, p=0.005), and LA active emptying fraction (r=0.29, p=0.002).

In stepwise linear regression analyses, LA active emptying fraction and CRP were weakly but significantly related with interatrial electromechanical delay (R^2=0.15, β=0.28, p=0.002 and β=0.25, p=0.006, respectively). There was no relationship between interatrial electromechanical delay and systolic blood pressure and LV mass index.

DISCUSSION

The present study showed that patients with RA had prolonged intra- and interatrial electromechanical delays measured with TDI and impaired LA mechanical functions and that interatrial electromechanical delay was associated with LA active emptying fraction and serum CRP level.

Rheumatoid arthritis is a systemic disease characterized by increased inflammatory activity. Several forms of cardiac involvement have been described in RA.[1-6,8,9] Accelerated coronary atherosclerosis, coronary vasculitis, superimposed coronary thrombosis, myocarditis, and pulmonary hypertension also contribute to rhythm disturbances in RA patients.[20] Atrial fibrillation is the most common arrhythmia encountered in clinical practice. Inflammation may have an important role in AF pathogenesis.[10,11] Several studies have demonstrated that P-wave dispersion, which is considered to be a risk factor for AF, is higher in patients with RA than control subjects, and prolonged P-wave dispersion is related with ongoing inflammation.[8,9]

Daubert et al.[21] demonstrated that the resultant electrophysiologic and electromechanical abnormalities were associated with a higher risk for AF. In addition to prolonged P-wave dispersion, interatrial electromechanical delay was related with increased risk for AF.[12,13] Atrial electromechanical delay can be measured with invasive or noninvasive methods.[8,9,12,13,22] With the progress in echocardiographic techniques, the time interval from P-wave onset to Doppler A-wave in each ventricle has been studied with Doppler echocardiography.[18,23,24]

Several studies have reported increased intra- and interatrial electromechanical coupling and atrial electromechanical delay, measured with TDI, in patients with paroxysmal AF, mitral stenosis, familial Mediterranean fever, and type 1 diabetes mellitus compared with control subjects.[13,18,23,24] These data suggest that increased interatrial electromechanical delay might be related with an increased risk for AF.[13,22,23] Consistent with our previous findings,[23] we showed that interatrial electromechanical delay was associated with serum CRP level. Although some studies found a relationship between LA dilatation and interatrial electromechanical delay,[13,18] such a relation was not observed in our study, possibly due to similar LA dimensions of the two groups.

Left atrial mechanical function is an important determinant of LV filling especially in patients with end-stage systolic and/or diastolic ventricular dysfunction, LV hypertrophy, and diminished LV enlargement capacity.[7] Although LV diastolic dysfunction is a frequently encountered complication in RA patients,[5,6] LA mechanical functions have not been studied in these patients. Left atrial mechanical functions consist of reservoir, conduit, and booster pump functions at different stages of cardiac cycle. The reservoir function takes effect during ventricular systole, passive conduit function in early diastole, and booster pump function during ventricular diastole in

the presence of sinus rhythm. In case of LV dysfunction, the left atrium could maintain sufficient cardiac output by regulation of atrial reservoir, conduit, and booster pump functions.[7] In our study, we found that LA mechanical functions were significantly impaired in RA patients. Thus, it is possible to consider that the decrease in LA passive emptying fraction is related to elevated end-diastolic LV pressure, and the increase in LA active emptying volume is associated with a compensatory mechanism in LA contraction. We also found that intra- and interatrial electromechanical delays were significantly prolonged in RA patients. Additionally, interatrial electromechanical delay was weakly but independently related with LA active emptying fraction and serum CRP level.

On the basis of our findings, we suggest that prolonged intra- and interatrial electromechanical delays and impaired LA mechanical functions may be an early form of subclinical cardiac involvement in RA patients who have no clinical evidence for cardiovascular disease. Hence, the risk of new and/or recurrent AF might be increased in RA patients.

The major limitation of our study is its cross-sectional design and lack of follow-up of the patients. The sample size was also relatively small. Patients could not be followed-up prospectively for arrhythmic episodes. Therefore, we do not know whether prolongation of intra- and interatrial electromechanical delays and impaired LA mechanical functions predict AF in RA patients. For this reason, long-term follow-up and large-scale prospective studies are needed to determine the predictive value of prolonged intra- and interatrial electromechanical delays in this population. The absence of diastolic function parameters was another potential limitation of our study.

In conclusion, our study suggests that intra- and interatrial electromechanical delays are prolonged and LA mechanical functions are impaired in RA patients, and that LA active emptying fraction and serum CRP level are independent factors of the interatrial electromechanical delay.

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