Echocardiographic Evaluation of Left Ventricular Function in Patients with Rheumatoid Arthritis

ROMATOİD ARTRİTLİ HASTALARDA SOL VENTRİKÜL FONKSİYONLARININ EKOKARDİYOGRAFİK DEĞERLENDİRMESİ

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Abstract

Objective: Rheumatoid arthritis (RA) is a systemic, inflammatory disease, which is associated with higher morbidity, and mortality rate compared with the normal population. One of the main causes for high mortality rate is the cardiac involvement during the disease course. The aim of this study was to evaluate the cardiac involvement in RA without clinic evidence of heart disease by conventional and new echocardiographic methods with special regard to disease activity and disease duration.

Material and Methods: The study included 82 patients diagnosed as RA according to the 1987 classification criteria of ARA. The patients and control subjects underwent 2-dimensional M-Mode and Doppler echocardiography in left decubitus position using HP Sonos 5500 instrument and multiHz probe.

Results: When we categorized the patients into two groups as those with disease duration of less and more than 5 years, there were a significant differences between the two groups in mitral E/A ratio (p= 0.009), tissue Doppler mitral annulus E'/A' ratio (p= 0.003) and Vp values (p= 0.004).

Conclusion: Diastolic dysfunction may develop especially in those patients with disease duration of more than 5 years. RA seems not to alter cardiac functions at least in the early periods of the disease. Our finding may explain the high incidence of cardiovascular disease observed in patients with longstanding RA.

Key Words: Arthritis, rheumatoid; heart diseases

Özet

Amaç: Romatoid artrit (RA) normal populasyonla kıyaslandığında morbidite ve mortalitesi yüksek bir hastalıktır. Hastalığın seyri sırasında kardiyak tutulum mortalite nedenlerinden biridir. Çalışmamızda RA belirgin klinik kardiyak hastalık olmadan konvansiyonel ve yeni ekokardiyografik yöntemlerle kardiyak tutulumu ve hastalık süresi ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: 1987 ARA kritelerine göre RA tanısı koyduğumuz 82 hasta değerlendirmeye alındı. Hastalar ve kontrol grubu 2-dimensional M Mode ve Doppler ekokardiyografi sol dekübit pozisyonda HP Sonos 5500 cihazında değerlendirildi.

Bulgular: RA'lı hastalar erken ve geç başlangıçlı olarak 2 gruba ayrıldı. Hastalık süresi 5 yıldan fazla olanlarda mitral E/A oranı (p= 0.009), doku doppler mitral anulus E'/A' oranı (p= 0.003) ve Vp değeri (p= 0.004) farklıydı.

Sonuç: Hastalık süresi özellikle 5 yıldan fazla olanlarda diyastolik disfonksiyon gelişebilir. RA erken dönemde kardiyak fonksiyonları etkilemiyor görünmektedir. Bizim bulgularımız uzun dönemdeki RA'da yüksek kardiyovasküler hastalık insidansını açıklayabilir.

Anahtar Kelimeler: Romatoid artrit; kalp hastalığı

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Rheumatoid arthritis (RA) is the most common inflammatory connective tissue disease. It is associated with increased morbidity and mortality.[1-3] In recent years, mortality rate due to RA has increased by at least two folds.[4] Among the leading causes of mortality due to RA are cardiovascular deaths such as ischemic heart disease as a result of accelerated atherosclerosis and stroke, with increasing rates in recent years.[5,6] It has been shown in necropsy studies that endocardial, myocardial and pericardial involvement may occur in patients with RA although no

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clinical signs and symptoms are evident. The most common cardiovascular findings are pericarditis and pericardial effusion.[5,7] Pancardial involvement, which results in cardiac failure via left ventricular systolic and/or diastolic dysfunction, has also been reported. Left ventricular diastolic dysfunction may result from impaired myocyte relaxation secondary to myocardial hypertrophy, interstitial fibrosis or ischemia. Valvular abnormalities, not compromising hemodynamic disorders, may also be detected with echocardiography in RA patients without any cardiac complaint.[2,3,7]

Previous echocardiographic studies have shown that diastolic dysfunction occurs in patients with RA.[8,9] These studies, however, had serious limitations and the systolic and diastolic function of the ventricles may be assessed better with the recently developed echocardiographical methods such as tissue Doppler echocardiography.

There is no comprehensive definition of early RA.[10] Presence of symptoms for shorter than 2 years (more conventionally, five years) indicates early disease.[11] In studies performed before biologic agents (e.g. infliximab, etanercept) were available, 50% of patients became disabled within 5 years of diagnosis.[12]

Therefore, in the present study, using conventional and recent echocardiographic methods, we aimed to evaluate cardiac function in patients with RA without any known cardiac diseases and to determine the relationship between cardiac function and activity and duration of the disease.

Materials and Methods

Patients

The study included 82 patients with active rheumatoid arthritis (RA) who were referred to our rheumatology out-patient clinic. Out of 82 patients, 67 were females and 15 males, whose diagnosis was based on the American Rheumatism Association 1987 revised criteria for the classification of RA.[13] Forty-seven healthy subjects (31 females and 16 males) comprised the control group. The mean age of the patients was 48±12 years (23-73 years). The mean age of the control group was 48±8 years (28-63 years). At the onset of the study, history was taken from all subjects and they all underwent physical examination and telecardiography, and if required, electrocardiography (ECG) and biochemical analyses to determine if they had any cardiac diseases (congenital cardiac malformation, coronary artery disease, arrhythmia or valvular heart disease), hypertension, diabetes mellitus, lung disease and other systemic diseases. These diseases were also used as exclusion criteria.

Complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor (with turbidimetric method), complete urinary analysis, fasting blood glucose determinations and hepatic and renal function tests were performed in the patients included in the study with active RA in order to evaluate the disease activity and systemic involvement.

Echocardiographic Evaluation

The patients and control subjects, in the left lateral decubitus position, underwent 2-dimensional, M-Mode and Doppler echocardiography with HP Sonos 5500 instrument equipped with 2.0 to 4.0 MHz, multiHz probe in accordance with American Society of Echocardiography criteria.[14] Systolic and diastolic diameters of the left ventricle were measured on the parasternal long axis view. Systolic and diastolic volumes of the left ventricle were determined according to the modified bi-planar Simpson method.[15] Ejection fraction (EF) of the left ventricle was calculated with the following formula;

EF= [(Diastolic volume-Systolic volume)/Diastolic volume] x 100.

Fractional shortening (FS) was calculated with the following formula;

FS= [(Diastolic internal diameter-systolic internal diameter)/diastolic diameter] x 100.

Diastolic functions of the left ventricle were evaluated in the apical four chamber view. Pulse wave Doppler sample volume was positioned at the tips of the mitral leaflets. Early filling wave velocity (E), late filling wave velocity (A), E/A ratio and E wave deceleration time (EDT) were measured. Pulse wave Doppler sample volume was placed between the mitral inflow and left ventricular outflow and transmitral and transaortic flow

profiles were recorded together. The time elapsing from the end of the transaortic flow to the beginning of the transmitral flow was accepted as isovolemic relaxation time (IVRT), and the time elapsing from the end of the transmitral flow to the beginning of the transaortic flow as isovolemic contraction time (IVCT) (Figure 1).

Colour M-mode flow propagation velocity was recorded in the apical four-chamber view, with the cursor aligned parallel to the inflow. Adjustments were made to obtain the longest column of flow from the mitral annulus to the apex. Flow propagation velocity (Vp) was determined as the slope of the first aliasing velocity from the mitral annulus into the left ventricle in early diastole (Figure 2).

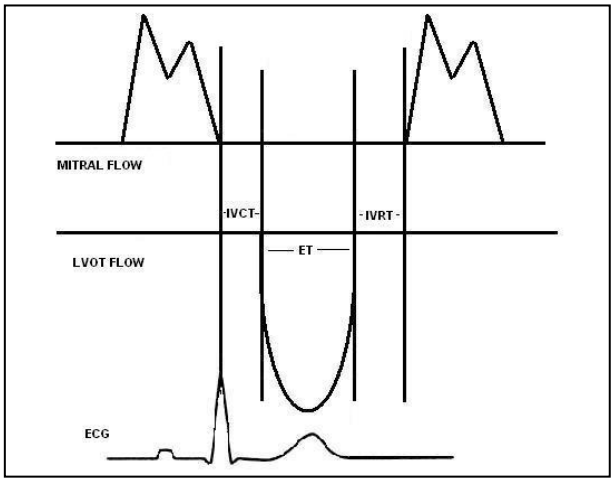

Figure 1. Measurement of IVCT and IVRT.

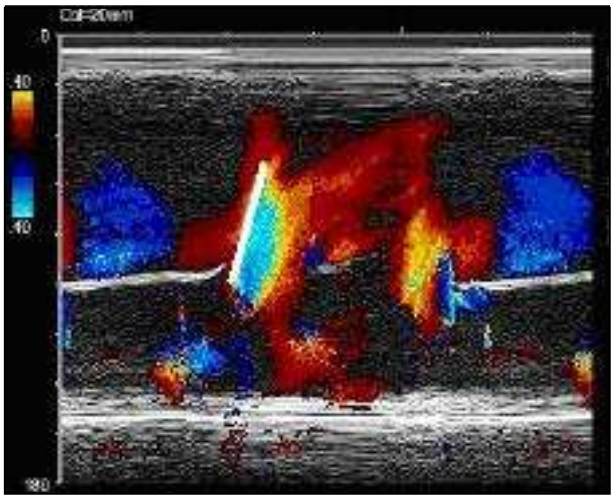

Figure 2. Measurement of Vp.

The pulmonary vein pulsed Doppler spectrum was obtained by placing the Doppler sample volume 0.5-1 cm into the right upper pulmonary vein.

Myocardial longitudinal function was assessed by tissue Doppler imaging on the four-chamber-view. Velocity profiles were recorded with a 1.7 mm sample volume placed at the lateral corner of mitral annulus. Care was taken to obtain an ultrasound beam parallel to the direction of the mitral annular motion. Filter settings were kept low and gains were adjusted at the minimal, optimal level to eliminate background noise and allow for clear signal. Peak early (E') and late (A') diastolic mitral annulus velocities and the E'/A' were obtained. Pulse wave tissue Doppler (PWTD) recordings were obtained on a strip chart recorder at a sweep speed of 50 mm/sec. PWTD velocities presented are the average of two to three cardiac cycles. A mean of five consecutive cycles was used for the calculations of all echo-Doppler parameters.

All echocardiographic recordings and analyses were carried out by the same investigator who was blinded to the patients.

We obtained approval for this research from the ethics committee of Adnan Menderes University.

Statistical Analyses

The statistical analyses were performed using the independent samples Student's t test in the SPSS software (10.0 version) and p values less than 0.05 were considered as significant.

Results

The mean age of the patients and the control subjects was 48 ± 12 years and was 48 ± 8 years respectively. The duration of the disease ranged from 1 to 30 years with a mean of 4.8 ± 5.2 years. When we categorized the patients into two groups; those with early RA (the disease duration of less than 5 years) and those with late RA (the disease duration of more than 5 years, there were significant differences between the two groups in mitral E/A ratio (p= 0.009), tissue Doppler mitral annulus E'/A' ratio (p= 0.003) and Vp (p= 0.004) values. These findings are shown in the Table 1.

Table 1. Comparison of echocardiographical findings in the patients with RA.

	Early RA (n = 55)	Late RA (n = 27)	p
Vp (cm/sec)	58± 8	52 ± 8	***0.004***
E'/A' (tissue Doppler)	0.93 ± 0.34	0.70 ± 0.22	***0.003***
Early diastolic (E)/late diastolic (A)	1.11 ± 0.37	0.90 ± 0.23	***0.009***
IVRT (ms)	79± 13	79± 13	> 0.162
EDT (ms)	196± 25	185 ± 22	> 0.346
Pulmonary diastole/systole	1	1	> 0.224
LVS (mm) (LV end systolic dimension)	30 ± 4	30 ± 3	> 0.783
LVD (mm) (LV end diastolic dimension)	47± 4	48 ± 5	> 0.602
EF (%)	68 ± 5	66 ± 6	> 0.403

With regard to the echocardiographical evaluation of the patient and control groups for cardiac involvement, there was no significant difference between the two groups in mitral E/A rate IVRT, EDT, pulmonary vein diastolic flow and pulmonary vein systolic flow rates ($p > 0.05$). No statistically significant differences were found in Vp value of color M-mode flow and tissue Doppler mitral annulus E'/A' ratio ($p > 0.05$).

Discussion

Cardiac involvement may occur as an extraarticular sign of RA. The prevalence of cardiovascular involvement can be up to 35%.[16] Cardiovascular diseases such as accelerated atherosclerosis[6] are the most common cause of mortality in RA. Although several studies reported diastolic dysfunction of the left ventricle, we did not find any alterations in both systolic and diastolic functions of the left ventricle in the patients with RA compared to the controls.

DiFranco et al[8] in their study on 32 patients with RA and Montecucco et al[9] in their study on 54 patients with RA found a lower rate of mitral E/A with conventional pulse Doppler and a lower rate of pulmonary vein systole/diastole than normal, which was an indication of diastolic dysfunction. However age,[17] heart rate,[17] gender,[18] systolic blood pressure,[19] preload and afterload[19] affect the determination of diastolic function and mitral flow E/A rate with conventional pulse Doppler and thus lower the specificity. Increased afterload initially alters the wall stress of the left ventricle as an adaptive mechanism. Long-term continuation of this adaptive mechanism increases the left ventricular wall thickness. Consequently, diastolic dysfunction occurs.[20]

Nishimura et al[17] evaluated diastolic dysfunction with conventional echocardiographic methods and emphasized the importance of heart rate and age. In fact, heart rate and age have important effects on ventricular filling and thus on mitral flow used for conventional echocardiographic evaluations. Increases in these parameters may lead to false results. Mitral regurgitation, although rare, affects the evaluation of diastolic function as well as pulmonary vein systolic and diastolic flows. Inappropriate placement of the transducer, contractile function of the atria and heart rate as well as PR interval on the ECG may lead to changes in these parameters. Flow in mitral regurgitation may alter the measurement by directing one of the pulmonary veins. It is impossible to measure PV in some patients.[18]

New methods have been developed to avoid significant constraints of conventional pulse wave Doppler methods in evaluation of diastolic function. The fact that Doppler measurements of mitral flow have far more limitations prompted utilization of color M-mode method in evaluating diastolic function. Vp measurement is performed with this method. Independence of Vp from preload increases its reliability in evaluating diastolic function.[17] Tissue Doppler technique is used reliably in evaluating diastolic function as it allows imaging through different acoustic windows from different segments of

the myocardium and as it is independent from preload.[20] Early diastolic myocardial velocity as measured with tissue Doppler is more sensitive than other Doppler and pulmonary vein flow parameters and provides important information about PV flow rates and mitral flow rates when used in evaluations of diastolic function.[21] For this reason, we used tissue Doppler and Vp methods in addition to conventional pulse wave Doppler method in order to detect diastolic dysfunction. Using tissue Doppler and Vp methods in addition to conventional pulse wave Doppler method improved the reliability of our study although invasive methods considered as gold standards were not used.[17-19] Using conventional echocardiographic methods, we observed diastolic dysfunction in the patients with RA. It may be explained by the disease duration as well as the increased specificity obtained with newer echocardiography methods.

DiFranco et al[8] reported that there was a correlation between mitral flow E/A rate and disease duration and that as disease duration prolonged, E/A rates decreased and much more severe diastolic dysfunction was found. We found the patients with RA to have disease duration of 9 years, while Montecucco et al reported disease duration of 5.9 years.[9] Maione et al[22] did not observe diastolic dysfunction with conventional echocardiographic methods in their study on 39 patients with RA with a mean disease duration of 7.1 years. However, they did not mention mitral flow Vp and mitral annular Doppler velocities in their study in which the disease duration was long.

Using conventional methods and Vp, Alpaslan et al[23] in their placebo controlled study on 32 patients with RA with a mean disease duration of 9 years and a mean age of 52 years found a reduction in mitral flow E/A rate, a prolongation in IVRT and an increase in mitral flow Vp and suggested that the patients with RA had diastolic dysfunction. Duration of the disease was long also in their study.

Our study included 82 patients with mean disease duration of 4.8 years and we used conventional methods reported in the literature (mitral flow E/A rate, IVRT, EDT, pulmonary vein flow systole/diastole rate) as well as such newer and current methods as mitral flow FPV, color Doppler M-Mode, mitral annular tissue Doppler velocities in order to evaluate left ventricular diastole function. Consequently, we did not find any left ventricular systolic or diastolic dysfunction with these methods in the patients with RA. However, when we divided the patients into two based on the disease duration, mitral flow E/A rate, mitral flow Vp, mitral annular tissue Doppler velocities indicated diastolic dysfunction in patients with a disease duration of longer than 5 years. Alpaslan et al[24,25] found a relation between diastolic dysfunction and disease duration and suggested a subclinical myocardial involvement. Also, Seyfeli et al[26] emphasized that a significant proportion of RA patients had impaired RV filling without overt heart failure. Impairment of RV diastolic function may be a predictor of subclinic myocardial and pulmonary involvement in patients with RA.

The results of this study contradict with those of others reported in the literature. In fact, we found the disease duration to be higher than that reported from other studies on patients with RA with diastolic dysfunction.[8,9,23] Although we did not observe diastolic dysfunction in the patients with RA, which is not consistent with the literature, mitral flow E/A rate, mitral flow Vp, mitral annular tissue Doppler velocities, all of which had higher specificities when the duration of the disease was longer than 5 years, showed diastolic dysfunction. However, it would be difficult to address whether this finding showed impairment due to advanced age or due to the effects of RA. Longer disease duration may impair diastolic function.[27]

In patients with RA without clinically evident cardiovascular disease, left ventricular diastolic function and right ventricular diastolic function are reduced.[28]

Canturk F et al demonstrated that combined use of Vp and intraventricular dispersion of E wave velocity could help the early detection of diastolic functions in patients with RA.[29]

In conclusion, diastolic dysfunction may develop especially in patients with disease duration of more than 5 years. RA does not seem to alter

cardiac functions at least in the early periods of the disease.

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