Original Article

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P Wave Dispersion in Juvenile Idiopathic Arthritis Patients With Diastolic Dysfunction

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Abstract

Objective: Cardiac involvement as pericarditis, myocarditis and valvular disease is common in juvenile idiopathic arthritis (JIA). However, there are few studies concerning systolic and diastolic functions of the left ventricle in children with JIA. P wave dispersion is a sign for the prediction of atrial fibrillation. A recent study found that rheumatoid arthritis patients had an abnormally high P wave duration and P wave dispersion, markers for supraventricular arrhythmogenicity. In this study, we aimed to evaluate P wave dispersion and its relation with diastolic dysfunction of the left ventricle in patients with JIA.

Methods: We performed electrocardiography and Doppler echocardiography on patients and controls. Maximum and minimum P wave duration were obtained from electrocardiographic measurements. P wave dispersion defined as the difference between maximum and minimum P wave duration was also calculated.

Findings: No statistically significant differences were found between the patients and controls in minimum, maximum P wave duration and P wave dispersion. Among the diastolic parameters in patients group, increased late flow velocity, decreased early flow velocity and prolonged isovolumic relaxation time reflected diastolic dysfunction.

Conclusion: During 12 months of follow-up, no supraventricular arrhythmias were documented in JIA with diastolic dysfunction. JIA with diastolic dysfunction has normal atrial conduction parameters and therefore seemingly do not have an increased risk of atrial fibrillation.

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Key Words: Juvenile idiopathic arthritis; Echocardiography; Arrhythmia; Diastolic dysfunction

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic autoimmune-autoinflammatory disease of unknown etiology. It is estimated that JIA affects up to 1 in 1,000 children worldwide and is the most common cause of autoimmune musculoskeletal disease in children[1]. It represents up to 65% of arthritic diseases in children and is one of the top five chronic illnesses in children[2]. Cardiac (pericardial, myocardial or endocardial) involvement is known to occur in patients with JIA, as it does in adults with rheumatoid arthritis (RA). Pericarditis is the most common and benign finding, occurring in 30% of the clinical population. Endocardium and

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myocardium are infrequently but more seriously involved, contributing to the morbidity and mortality of the disease[3]. Myocarditis can be life-threatening with congestive heart failure and arrhythmias[3]. Cardiac repolarization abnormalities may be seen due to cardiac involvement in RA. Recently, a study associated with P wave dispersion (PWD) has been reported in patients with RA. P dispersion is a determinant of supraventricular arrhythmias[4]. PWD is defined as the difference between the longest and shortest P wave duration recorded from multiple surface electrocardiographic leads[5]. An increase in PWD is presumed to be associated with heterogeneity in atrial conduction, in addition to posing a risk of occurrence and recurrence of atrial fibrillation (AF)[5,6]. PWD has been found to serve as a specific and sensitive marker in various clinical settings[5]. In a previous study, p-wave dispersion, has been indicated to increase at left ventricular diastolic dysfunction[7].

Although based upon these putative relationships between JIA and cardiac involvement mentioned above, no research study has been performed yet to evaluate the P wave duration and PWD in JIA patients. Therefore, the aim of the present study was to investigate the P wave duration and PWD in JIA patients with diastolic dysfunction and to evaluate their relation with echocardiographic parameters.

Subjects and Methods

Study design and patients

This cross-sectional study was conducted at the Department of Pediatric Rheumatology in Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey. Prior to subject recruitment, the study protocol was reviewed and approved by the local ethics committee, in accordance with the ethical principles for human investigations, as outlined by the Second Declaration of Helsinki and written informed consents were obtained from all the patients or their proxies. From August 2009 to September 2010 consecutively 50 JIA patients with diastolic dysfunction and age-gender matched 70 healthy children were recruited to the study.

All study subjects were divided into 2 groups; group 1 (n=50) consisted of JIA patients with diastolic dysfunction, and group 2 (n=70) consisted of healthy children. The exclusion criteria were as follows: children who were older than 16 years and younger than 5 years; children with congenital or rheumatic heart disease; diabetes mellitus; children with history of any clinical evidence of coexisting cardiac disease; diastolic dysfunction detected with echocardiography, arrhythmia, valvular heart diseases or ischemic heart diseases were excluded. All of the patients had sinus rhythm in electrocardiographic measurement. All of the study subjects underwent a detailed echocardiography and standard electrocardiography when they were clinically in the remission phase.

Baseline definitions and measurements

All of the patients fulfilled the International League against Rheumatism criteria for diagnosis and classification of JIA[8]. Height and weight were directly measured by using a standardized protocol. Erythrocyte sedimentation rate (ESR, mm/h) was determined by the Westergen method.

Echocardiographic examination

A detailed echocardiography, which included an M-mode, two dimensional, color and Doppler (continuous and pulse wave) examination. Images were obtained on a Siemens Acuson CV70 with a 4-2 MH transducer. The patients were requested to rest for 5 min before the measurements and breathe slowly during the procedure. Recordings were performed with subjects in the supine or left lateral positions. M-mode tracings were obtained at the level of tips of mitral leaflets in parasternal long axis position and measurements of left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD) were performed according to the recommendations of the American Society of Echocardiography[9]. Ventricular septal and posterior wall thickness at end-diastole, and left atrial dimension (LAD) were measured from parasternal long axis window in M-mode echocardiography. Left ventricular ejection fraction (EF) and fractional shortening (FS) were obtained using Teichholtz in M-mode

echocardiography[10]. LV diastolic function was assessed by measuring the mitral flow velocity recorded in the apical four-chamber view. The pulse Doppler sample volume was placed in the left ventricular inflow tract at the level of mitral leaflet tips and three consecutive measurements were averaged. The various variables of diastolic function that were measured included: (1) peak early (E; m/sec) and peak atrial filling velocity (A; m/sec), (2) ratio of E to A (E/A), (3) E decelaration time (Edt; m/sec), (4) isovolumic relaxation time (IVRT; m/sec). This last parameter was measured with the probe at the apical 5-chamber position with the sample volume placed between the aorta and mitral valve where the recordings of both valves were taken simultaneously.

2.4. Electrocardiographic examination

The 12-lead electrocardiography (ECG) was recorded at a paper speed of 25 mm/s and gain of 10 mm/mV (Cardiofax V, Nihon Kohden Corp., Tokyo, Japan) in the supine position and were breathing freely but not allowed to speak during the electrocardiographic recording. Electrodes were placed in anatomical positions according to routine procedure. ECG strips were recorded for 10 second with a standard device. ECGs of inadequate quality were repeated. To avoid from diurnal variations, the ECG recordings of all JIA patients and controls were performed at the same time interval (09:00-12:00 hours). The onset of the P wave was defined as the point of first visible upward departure from baseline for positive waveforms, or as the point of first downward departure from baseline for negative waveforms. The return to the baseline was considered the end of the P wave. P wave duration was measured from the onset to the offset of the P wave. The patients were excluded if these points were not clear. Maximum P wave duration is defined as the longest P wave duration and minimum P wave duration is defined as the shortest P wave duration. PWD defined as difference between maximum P wave duration and minimum P wave duration was also calculated. All the measurements were repeated three times and average values were accepted for each of electrocardiographic parameters. All of the measurements were performed by two experienced investigators unaware of the subject's clinical status. The blinded intra and inter-observer variability of P wave measurements were <5%. Patients were followed for 1 year.

2.5. Statistical analyses

All statistical analyses were performed using SPSS for Windows version 11.0 (SPSS, Chicago, IL, USA). *Kolmogorov-Smirnov* tests were used to test the normality of data distribution. Continuous variables were expressed as mean values plus or minus standard deviation, and categorical variables as percentages. The chi-square test was used to compare the categorical variables between groups. Independent sample t-test was used to compare continuous variables between groups. Pearson's correlation analysis was used to examine the association between sedimentation rate and electrocardiography findings in patients with JIA. Two-sided *P* value < 0.05 was considered statistically significant.

Findings

The demographic, clinical and laboratory characteristics of the study population are summarized on Table 1. There were no significant differences between the two groups with regard to

Table 1: Comparison of demographic, laboratory and clinical characteristics of the study subjects

Parameter	Group 1 (n=50)	Group 2 (n=70)	*P* value$^{\alpha}$
Age (years) [Mean (SD)]	10.51 (3.42)	9.92 (2.79)	NS
Boys/Girls	24/26	33/37	NS
Height (cm) [Mean (SD)]	134.67 (18.55)	135.33 (17.82)	NS
Weight (kg) [Mean (SD)]	34.32 (14.42)	35 (14.11)	NS
Body surface area (m^2) [Mean (SD)]	1.11 (0.31)	1.13 (0.21)	NS
ESR (mm/hour) [Mean (SD)]	27.61 (18.22)	10.22(4.10)	< 0.001

SD: standard deviation; ESR: Erythrocyte sedimentation rate; NS: Non significant; α: By independent sample t test

Table 2: Comparison of cardiovascular parameters between groups

Parameter	Group 1 (n=50) Mean (SD)	Group 2 (n=70) Mean (SD)	*P* value[α]
Heart rate (beat/min)	89.52 (17.71)	87.43 (15.20)	NS
Systolic BP (mmHg)	103.34 (12.52)	101.23 (12.89)	NS
Diastolic BP (mmHg)	69.24 (8.82)	68.11 (7.63)	NS

SD: standard deviation; BP: blood pressure; NS: Non significant. A: By independent sample t test

gender, age, body surface area. Erythrocyte sedimentation rate (ESR, mm/h) was significantly higher in the patients with JIA compared to controls. Mean ESR at the end of one hour was 27.61±18.22 mm/hr in JIA patients. Mean disease duration was 44.83±35.87 months. JIA was of the polyarticular type in 13/50 (26%), oligoarticular in 22/50 (44%), systemic type in 5/50 (10%), enthesitis related-arthropathy in 6/50 (12%), and psoriatic in 4/50 (8%) (Table 1). All patients were free from cardiovascular symptoms. Table 2 shows the cardiovascular parameters in JIA patients and controls. There was no significant difference in heart rate, systolic and diastolic blood pressures between patients and controls. LV end-diastolic dimension, LV end-systolic dimension, left atrium dimension, aortic dimension and LV ejection fraction (EF), fractional shortening (FS) showed nonsignificant difference between the JIA and control group (Table 3). Among diastolic measurements all parameters showed significant differences between the patients and control group. Peak E value was significantly lower, and peak A value was significantly higher so that E/A ratio was significantly decreased in patients versus controls. Diastolic times (Edt and IVRT) were prolonged in JIA patients (Table 4).

The calculated P wave duration and PWD parameters for the two groups are shown in Table 5. There was no statistically significant difference in maximum and minimum P wave duration. PWD was also similar between JIA patients with diastolic dysfunction and controls. In addition, there was no significant correlation between erythrocyte sedimentation rate (millimeter/hour) and PWD (r=-0.088, P=0.3). During 1 year of follow-up, no case of atrial fibrillation was documented in patients group.

Discussion

Cardiac involvement is common in JIA and it is the second major cause of mortality in this disease[3,12]. The mortality rate in rheumatoid arthritis is between 0.29% and 4.2%[13,14]. Mortality rates in patients with rheumatoid arthritis (RA) have been reported to be higher than for the general population[15]. Ischemic heart diseases, hypertension and myocarditis are common causes of mortality; therefore, it is important to follow these patients through childhood.

Table 3: Comparison of echocardiographic findings of the study subjects

Parameter	Group 1 (n=50)	Group 2 (n=70)	*P* value[α]
LV-EDD (mm) [Mean (SD)]	39.50 (6.12)	38.72 (6.01)	NS
LV-ESD (mm) [Mean (SD)]	24.23 (4.43)	24.30 (3.84)	NS
IVS thickness (mm) [Mean (SD)]	6.73 (1.32)	7.11 (0.83)	NS
Posterior wall thickness (mm) [Mean (SD)]	7.24 (1.43)	7.20 (0.89)	NS
Left atrial dimension (mm) [Mean (SD)]	25.82 (4.19)	25.49 (3.98)	NS
Aort dimension (mm) [Mean (SD)]	24.32 (2.16)	23.29 (2.88)	NS
LV-EF (%)	64.50 (7.21)	66.20 (6.41)	NS
LV-FS (%)	39.50 (6.12)	38.72 (6.01)	NS

SD: standard deviation; NS: Non significant; LV-EDD: left ventricular end-diastolic diameter; LV-ESD: left ventricular end-systolic diameter; IVS: interventricular septum; LV-EF: Left ventricular ejection fraction; LV-FS: Left ventricular fractional shortening; α: by independent sample t test

Table 4: Comparison of diastolic parameters using Doppler echocardiography

Parameter	Group 1 (n=50) Mean (SD)	Group 2 (n=70) Mean (SD)	*P* value$^{\alpha}$
E (m/s)	0.86 (0.08)	1.10 (0.19)	< 0.001
A(m/s)	0.68 (0.07)	0.51 (0.11)	< 0.001
E/A	1.31 (0.15)	2.01 (0.24)	< 0.001
Edt (ms)	122 (19.11)	110.12 (6.74)	< 0.001
IVRT (ms)	94 (15.21)	76 (9.48)	< 0.001

SD: standard deviation; E: peak early diastolic flow velocity; A: peak late diastolic flow velocity; Edt: early diastolic flow deceleration time; IVRT: isovolumic relaxation time; α:By independent sample t test

In this study, JIA patients had no demonstrated cardiac symptoms. Although heart rate was higher in JIA patients than in controls, there was no significant difference. This mild increase in heart rate could be related to the inflammatory mediators release of the disease or the onset of myocarditis. This is in agreement with the study of Oguz and his group[3], but Bharti et al[16] found that the heart rate is significantly increased.

Also, our patients had nonsignificantly higher systolic-diastolic blood pressure when compared with control group. But such mild difference in childhood may lead to onset of overt hypertension on age advances. The explanation of this might be related to steroid therapy and non-steroidal anti-inflammatory drugs intake, which lead to salt and water retention[13]. This tendency to increased blood pressure should be closely monitored during follow-up. Mustonen et al[17] studied 12 asymptomatic adults with RA and found no changes in heart rate or blood pressure, as in our study.

Our data did not demonstrate any significant differences in the LVESD, LVEDD, EF and FS. Alkady et al[13] in their patients series demonstrated significantly enlarged LVEDD and insignificantly reduced systolic function parameters (EF, FS) compared to controls but were within normal limits. In a study of patients with JIA, also, Oguz et al[3] reported higher LVESD and lower EF as compared to controls. However, like our study, they did not find any significant differences in the resting heart rate or LVEDD. In a study of 35 patients with JIA, Bharti et al[16], also reported significant higher LVESD and LVEDD. Udayakumar et al[18], in their study carried out on adult RA patients, found a significant increase in LVESD and LVEDD but with no significant difference in EF and FS. We found abnormalities in diastolic function. E was decreased while A was increased in velocity. The E/A ratio was lower and IVRT was longer in the patient group. Our data are consistent with the data of Oguz et al[3]. Bharti et al[16], Alkady et al[13], and Huppertz et al[19], reported that late diastolic flow velocity was significantly increased in patients with HLA B27-associated JIA at the termination of exercises. This is in contrast to our results where we noted diastolic dysfunction at rest. Also Vlahos et al[20] did not find any cardiac diastolic dysfunction in a series of JIA patients and concluded that cardiac diastolic dysfunction appears to be a later finding. Mustonen et al[17] studied 12 asymptomatic adults with rheumatoid arthritis and found prolonged IVRT and decreased E values indicating diastolic dysfunction despite normal systolic function, as in our study. These abnormalities could theoretically be due to a decrease in preload, to an increase in afterload, or to impaired relaxation of the left ventricle, probably due to a myocardial fibrotic

Table 5: Comparison of electrocardiographic measurements of the study subjects

Parameter	Group 1 (n=50) Mean (SD)	Group 2 (n=70) Mean (SD)	*P* value$^{\alpha}$
Maximal P wave duration (ms)	76.92 (11)	81.31 (9.11)	NS
Minimal P wave duration (ms)	55.20 (11.12)	56.63 (10.41)	NS
P wave dispersion (ms)	24.42(11.40)	25.62 (10.24)	NS

SD: standard deviation; NS: Non significant; α: By Independent sample t test

process. In a comment by Gupta and Rao[21], they stated that increasing diastolic dysfunction has been found with increased duration of the disease, but the etiology of this diastolic dysfunction is still unclear. The diastolic dysfunction found in this study is usually seen in systemic hypertension, ischemic heart disease and cardiomyopathy. Our completely asymptomatic, young patients had no electrocardiographic abnormalities resembling ischemia. Thus, the cause of abnormal diastolic parameters may be multiple and cumulative effect of several factors. Diastolic dysfunction might appear years before overt cardiac dysfunction becomes apparent.

We hypothesized that PWD may be not only affected in patients with Rheumatiod Arthritis but also may be affected in JIA patients with diastolic dysfunction. Therefore we investigated PWD in JIA patients with diastolic dysfunction. To our knowledge, no previous study has been performed to compare P wave duration and PWD changes in JIA patients. This study showed that JIA patients with diastolic dysfunction had similar P wave length and PWD on healthy controls. Our findings disagree with Guler et al[4]'s recent study comparing electrocardiographic parameters of RA patients and controls. They reported that the RA group had a significantly higher maximal P wave duration (110 ± 8 vs. 104 ± 10 ms, P=0.03) and higher PWD (42±12 vs 31±9 ms, *P*=0.001). The authors speculated that the diastolic dysfunction of RA contributed to the abnormal atrial conduction and the seemingly increased risk of atrial arrhythmias. Our results are supported by lack of an increased risk for atrial fibrillation in JIA which is common in the medical literature. The results of present study suggested in relation of PWD that JIA patients with diastolic dysfunction not under the risk for atrial arrhythmias. Maybe, further studies are necessary to investigate the frequency of atrial arrhythmias by rhythm Holter in JIA patients.

In our study, inflammatory marker (erythrocyte sedimentation rate) was significantly higher in JIA patients than in control subjects. But there was no significant correlation between erythrocyte sedimentation rate (millimeter/hour) and PWD. This incompatibility in our patients might be explained due to the short disease period.

Conclusion

The findings of the present study showed that the evaluation of electrocardiographic findings may be more accurate if it was performed during both exacerbations and attack-free periods for assuming that PWD is affected in JIA patients. Long term follow-up is required before definitive conclusions can be made. In this study, we used manually measured PWD. In future the dispersion of repolarization may be assessed invasively using endocardial or epicardial mapping, or non-invasively by multilead body-surface mapping. Several limitations should be considered in the present study. Firstly, the sample size was relatively small, and design of the study is cross-sectional. Therefore, the results of the present study suggested that large-scale, prospective, longitudinal studies are needed to assess the effect of electrocardiographic studies on the risk of malignant supraventricular arrhythmia and sudden cardiac death in this special patient population.

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Conflict of Interest: None

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