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ORIGINAL ARTICLE

Assessment of cardiac and pulmonary function in children with juvenile idiopathic arthritis

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Abstract Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disorder of childhood. It is a group of diseases characterized by chronic synovitis and associated with many extra-articular manifestations including cardiac and pulmonary involvement. Cardiac involvement as pericarditis, myocarditis and valvular disease is common in JIA. There are, however, few descriptions concerning systolic and diastolic functions of the left ventricle (LV) and the development of lung disease in children with JIA. The study was carried out to detect the cardiac and pulmonary involvement and to study the systolic and diastolic function of the left ventricle in a group of children with juvenile idiopathic arthritis. Forty-five children with JIA without any cardiac or pulmonary symptoms and 30 age- and sex-matched controls were included in the study. M-mode, two-dimensional and pulsed Doppler echocardiography (ECHO) was performed on 36 patients. Tissue Doppler ECHO examination was performed on 24 patients to assess systolic and diastolic functions of left ventricle. Pulmonary function tests: Forced vital capacity (FVC%), the predicted forced expiratory volume in the first second (FEV_1%) and FEV_1/FVC ratio and peak expiratory flow (PEF), total lung capacity (TLC) and residual volume (RV), carbon monoxide diffusing capacity of the lung (DLCO) and DLCO/alveolar volume (VA) were evaluated in 32 patients. Informed consent was obtained from all children's parents. The study protocol was approved by ethical committee of Faculty of Medicine, Assiut University. In this study, children with JIA had higher systolic and diastolic blood pressures, resting heart rate, left ventricle systolic size and volume (4.35 ± 0.68 vs. 3.92 ± 0.28, P value = 0.02). On Doppler and tissue Doppler analysis, the JIA group had lower peak early filling velocity (E, m/s), higher peak atrial filling velocity (A, m/s) and prolonged diastolic E and A waves deceleration times and isovolumic relaxation time (IRT) compared to control. Regarding pulmonary function tests, children with JIA showed significant decrease in FVC, PEF, Pimax, Pemax and DLCO compared to normal controls. This decrease was not related to age, height or weight of these patients. There was significant inverse correlation between lung function parameters and the rheumatoid factor titer, erythrosedimentation rate, disease duration and the duration of methotrexate use ($P < 0.01$). Despite of an asymptomatic cardiopulmonary status, significant systolic and diastolic functional abnormalities exist in children with JIA. Also, both restrictive and obstructive lung impairments were found.

Keywords Juvenile idiopathic arthritis · Echocardiography · Pulmonary function tests

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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 disease in children and one of the top five chronic illnesses in children [2]. Extraarticular manifestations of JIA include an erythematous skin rash, fever, hepatosplenomegaly and cardiovascular and pulmonary lesions, usually occurring in systemic-onset JIA [3].

Cardiac involvement in the form of pericarditis, pericardial effusion, myocarditis and vulvular disease is well documented in JIA [4–7]. Pericarditis in JIA is the most common and benign finding of cardiac involvement occurring in 30% of the JIA patients and predominately in children with the systemic form of JIA [8, 9]. Endocardium and myocardium are infrequently but more seriously involved, contributing to the morbidity and mortality of the disease [9]. Most patients with endocarditis have aortic regurgitation, and others have mitral regurgitation, which can occasionally require valve surgery [10]. Myocarditis can be life-threatening with congestive heart failure and arrhythmias [9].

Pulmonary parenchymal involvement is very uncommon [11, 12]. Many investigators have reported pleural and pulmonary involvement in adult rheumatoid arthritis, including pleural effusions and thickening, necrobiotic rheumatoid nodules, fibrosing alveolitis, and increased incidence of bronchiectasis, bronchitis and pneumonia. However, similar respiratory complications are rather uncommon in JIA [13]. On the other hand, Camiciottoli et al. [14] reported that the lung in some cases of JIA is a target of the disease. Pneumonitis and pleuritis are the most frequent respiratory abnormalities; transient or persistent pulmonary infiltrates have also been reported, especially in systemic JIA. While respiratory function in adults with rheumatoid arthritis (RA) has been extensively investigated, few studies have been carried out in JIA children.

Objectives

- To detect cardiac and pulmonary involvement in a group of children with JIA without clinical symptoms and/or radiological signs of cardiac or pulmonary affection.
- To study the systolic and diastolic functions of the left ventricle in the same group.
- To find the effect of the MTX therapy on pulmonary functions of JIA patients.

Patients and methods

The study was carried out on 45 patients (21 boys and 24 girls) recruited from Rheumatology and Rehabilitation department, Faculty of Medicine, Assiut University. All of the patients fulfilled the International League against Rheumatism criteria for diagnosis and classification of JIA [15]; aged from 5 to 16 years old (mean 13.28 ± 2.84 years). Children excluded from the study were those older than 16 years and younger than 4 years, children with congenital or rheumatic heart disease and with diabetes mellitus or systemic hypertension. Also, children with history of any clinical evidence of cardiac or pulmonary manifestations, chronic lung diseases, coronary artery diseases, arrhythmia, valvular heart diseases or ischemic heart diseases have been excluded.

Thirty apparently healthy age- and sex-matched children (16 boys and 14 girls) aged from 9 to 16 years old (mean 12.16 ± 2.05) were enrolled in the study and served as control group.

All patients had complete medical history, physical and articular examinations. Most of patients had a prolonged history of treatment with non steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), and some patients received 40 mg prednisone to control the disease activity.

The following laboratory tests were performed to all patients: anti-streptolysin O titer (ASOT), full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF). Echocardiogram (ECHO) was performed to 36 patients, and pulmonary function tests were performed to 32 patients from the patients group. Control group and 23 patients from the ECHO and pulmonary functions groups had done both the ECHO and pulmonary functions tests.

Informed consent was obtained from all children or their relative. The study protocol was approved by ethical committee of Faculty of Medicine, Assiut University.

Echocardiographic examination

Echocardiography was performed in 36 patients. Each patient underwent an echocardiographic examination using an M-mode, two-dimensional and pulsed Doppler modalities. In addition, 24 patients underwent tissue Doppler echo examination. Images were obtained on a Hewlett-Packard Sonos 4500 echocardiogram with a 4.0-MHz transducer. Recordings were done with the subject in the supine position and breathing freely. M-mode tracings were obtained at the level of the papillary muscles in the parasternal long axis or short axis positions, and measurement was taken according to the American society of cardiology recommendations [16]. The following measures were obtained: interventricular septal thickness in diastole (IVSd), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) and left ventricular posterior wall thickness in diastole (PWTd). Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic

volume (LVESV), fractional shortening (FS) and ejection fraction (EF) were calculated from these data using Teicholz method digitally. After the two-dimensional and M-mode examination, mitral flow was obtained from apical 4-chamber view using pulsed-wave Doppler echocardiography. The sample volume was placed in the left ventricular inflow tract at the level of the mitral leaflet tips. Then, tissue Doppler tracing was obtained in the apical 4-chamber view at the level of the medial or lateral mitral valve annulus. Three consecutive measures were averaged to avoid differences due to respiration.

Variables of diastolic function included the follows: (1) peak early (E, m/s) and peak atrial filling velocity (A, m/s), (2) the ratio of E to A (E/A), (3) E acceleration time (Eat, ms), (4) E deceleration time (Edt, ms), (5) E duration (Edur, ms), (6) E deceleration slope (EFslp, m/s²). (7) A acceleration time (Aat, ms), (8) A deceleration time (Adt, ms) and (9) isovolumic relaxation time (IRT, ms). This last parameter was measured with the probe at the apical 5-chamber position with the sample volume was placed between the aorta and mitral valve where the recordings of both valves were taken simultaneously. Finally, using tissue Doppler echocardiogram, three waves were systolic S wave (cm/s), diastolic E wave (cm/s) and diastolic A wave (cm/s). Then, isovolumic relaxation time was measured as the distance between the S wave and E wave (IRT, ms).

Pulmonary functions tests

Pulmonary function testing was performed in only 32 patients who could complete the test, utilizing Sensor Medics Corporation Spirometer (Model CA92687, SN 54065, Osaka, Japan) to measure the predicted forced vital capacity (FVC%), the predicted forced expiratory volume in the 1st second (FEV_1%) and FEV_1/FVC ratio and peak expiratory flow. Each measurement was repeated at least 3 times, and the highest acceptable measurement was compared with normal predicted values. Total lung capacity (TLC) and residual volume (RV) were measured using standardized plethysmography (ZAN, Germany). Carbon monoxide diffusing capacity of the lung (DLCO) and DLCO/alveolar volume (VA) were determined using standardized single-breath technique. Reference values from the European Community for Steel and Coal (for DLCO) and reference values obtained in a Dutch population of healthy children aged 6–18 were used.

Respiratory muscle strength was assessed by measuring maximum static respiratory mouth pressures with a tube mouthpiece attached to a pressure gauge. The Pimax was measured by having the child exhale to near residual volume followed by maximal inhalation effort. The Pemax was measured by having the child to inhale to near TLC followed by maximal exhalation effort. Each child performed at least three measurements. The highest value obtained was reported.

Data analysis

All data are expressed as the mean ± standard deviation (SD). A two-tailed paired *t*-test was used for statistical comparisons by SPSS version 16 (The Statistical Package for the Social Science Program). Significance was considered according to the level of (*P*-value) as follows: $P > 0.05$ = not significant, $P \leq 0.05$ = significant, $P \leq 0.01$ = highly significant and $P \leq 0.001$ = very highly significant.

Results

The demographic characteristics of the study population are summarized in (Table 1).

Table 2 represented the clinical and laboratory characteristics of the JIA patients.

None of the patients had any symptoms or signs related to cardiovascular involvement nor were there any abnormal auscultatory findings among them. Table 3 showed the cardiovascular parameters in JIA patients and controls. Regarding echocardiography, the pericardium was thickened with thin film of effusion in 6 (16.2%) patients. The mitral valve was thickened with trace or mild regurge in 9 (24.3%) patients, while the aorta was thickened only in 2 (5.4%) patients with no regurge (Table 4). Regarding parameters of left ventricular systolic function, LVEDV and LVEDD were significantly larger in JIA patients compared to control, while LVESV and LVESD were insignifi-

Table 1 Demographic data of the study population

	JIA patients	Controls
No	45	30
Sex		
Boys/girls	21/24	14/16
Age (years)		
Mean ± SD	13.28 ± 2.84	12.16 ± 2.05
Range	5–16	9–16
Height (cm)		
Mean ± SD	139.86 ± 22.55	137.86 ± 11.31
Weight (kg)		
Mean ± SD	40.37 ± 16.36	36.26 ± 9.45

JIA juvenile idiopathic arthritis, *No* number, *cm* centimeters, *kg* kilogram

Table 2 Clinical and laboratory data of JIA patients

	JIA patients
Duration of disease (m)	
Mean ± SD	43.51 ± 32.22
Type of onset (no, %)	
Oligoarticular	5, 11.1%
Polyarticular	10, 22.2%
Systemic	9, 20%
Enthesitis-related arthropathy	20, 44.4%
Psoriatic	1, 2.2%
Disease activity	
Active/inactive	27/18
Serological characteristics	
ESR mm/hr(1st h)	
Mean ± SD	39.88 ± 28.90
RF positive	
No/total (%)	4/45 (8.9%)
Medication	
MTX	
No/total (%)	26/45 (57.8%)
Duration of MTX (mon)	
Mean ± SD	23.42 ± 16.27
Current steroids	
No/total (%)	8/45 (17.8%)

No number, *m* months, *ESR* erythrosedimentation rate, *1st hr* first hour (3–5 in men, 7–12 in women), *MTX* methotrexate

Table 3 Cardiovascular parameters in JIA patients and controls (mean ± SD)

Item	JIA ($n = 36$)	Controls ($n = 30$)	*P* value
Heart rate (beat/min)	85.35 ± 9.16	80.37 ± 6.46	<0.05
Systolic blood pressure (mmHg)	113.5 ± 8.35	105.9 ± 7.7	<0.001
Diastolic blood pressure (mmHg)	72.81 ± 7	66.46 ± 6.87	<0.001

Table 4 Doppler echocardiographic findings in JIA patients and controls (no/%)

Item	JIA ($n = 36$)	Controls ($n = 30$)
Pericarditis with effusion	6 (16.22%)	0
Hypokinesis	0	0
Aortic affection	2 (5.4%)	0
Mitral affection	9 (24.3%)	0

cantly larger, and FS and EF were insignificantly lower in patients compared to control group (Table 5).

On the other hand, among diastolic measurements, most of parameters showed significant differences between the

Table 5 Systolic parameters measured by M-mode echocardiography

Systolic parameter	JIA group	Control group	*P* value
LVEDD (cm)	4.35 ± 0.68	3.92 ± 0.28	0.02
LVESD (cm)	2.76 ± 0.44	2.66 ± 0.19	0.3
LVEDV (ml)	92.74 ± 17.77	78.76 ± 13.64	0.008
LVESV (ml)	33.4 ± 6.68	29.9 ± 12.4	0.39
FS	31.2 ± 2.4	31.7 ± 3.5	0.7
EF	58.6 ± 4.9	59.9 ± 2.9	0.8

Table 6 Diastolic parameters measured by Doppler echocardiography

Diastolic parameter	JIA group	Control group	*P* value
E (m/s)	0.87 ± 0.07	1.08 ± 0.105	0.000
A (m/s)	0.67 ± 0.069	0.52 ± 0.102	0.000
Eat (ms)	0.79 ± 9.9	84.0 ± 11.4	0.2
Edt (ms)	123 ± 20.8	111.5 ± 11.8	0.043
Edur (ms)	209 ± 26.9	191.5 ± 18.7	0.044
E/Fslp (m/s^2)	768.7 ± 190.4	936.3 ± 125.02	0.008
Aat (m/s)	60.0 ± 10.26	63.5 ± 7.45	0.24
Adt (m/s)	85.0 ± 12.35	75.5 ± 6.86	0.007
E/A	1.302 ± 0.168	2.06 ± 0.277	0.000
IRT (ms)	93.5 ± 14.96	77.5 ± 10.96	0.000

Table 7 Diastolic parameters measured by tissue Doppler

Tissue Doppler	JIA Group	Control group	*P* value
S wave	12.73 ± 0.89	13.49 ± 2.29	0.18
E wave	18.2 ± 2.1	25.5 ± 2.06	0.000
A wave	12.83 ± 1.3	9.26 ± 2.06	0.000
IRT	81.0 ± 11.19	72.5 ± 8.5	0.006

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 control. Diastolic times were significantly prolonged in JIA patients including E and A waves deceleration times (total E wave duration and IRT), while E and A acceleration times were insignificantly shortened in the patients group. As a result, the E/F slope decreased in our patients group (Table 6). Regarding the tissue Doppler modality, parameters were summarized in Table 7.

Lung function results are presented in (Table 8). FVC, FEV_1, PEF and DLCO were significantly lower in diseased group (active and inactive) compared to normal controls. FEV1/FVC, RV and TLC were not different from the controls. Pimax and Pemax were significantly lower in patients compared to controls. The reduction in FVC, FEV_1, PEF, DLCO were not related to age, height or weight of the

Table 8 Pulmonary function tests and respiratory muscle function parameters in the studied population

Values	Active JRA ($N = 15$)	Inactive JRA ($N = 15$)	Controls ($N = 30$)	P value
FVC%, mean ± SD	74.8 ± 19.1	76.7 ± 24.1	92.0 ± 6.3*	<0.00305*
FEV_1%, mean ± SD	71.3 ± 21.5	78.0 ± 22.8	90.9 ± 5.6*	<0.05*
FEV_1/FVC%, mean ± SD	85.7 ± 19.7	83.1 ± 16.6	81.7 ± 4.2	NS
PEF%, mean ± SD	66.4 ± 27.4	69.2 ± 31.0	89.5 ± 6.3*	<0.05*
RV%, mean ± SD	87.4 ± 45.0	106.3 ± 38.1	95.0 ± 4.5	<0.05*
TLC%, mean ± SD	81.6 ± 19.2	93.9 ± 16.0	94.0 ± 4.3	<0.05*
DLCO%, mean ± SD	81.4 ± 26.0	87.7 ± 2.3	97.8 ± 7.3*	<0.05*
Pemax%, mean ± SD	63.3 ± 31	66.5 ± 14	84.6 ± 12.9*	<0.05*
Pimax%, mean ± SD	62.2 ± 12.9	67.9 ± 21.9	96.3 ± 2.3*	<0.05*

* $P < 0.05$

Table 9 Correlations between lung function parameters, clinical and laboratory characteristics of the studied group

	FVC	FEV_1	PEF	DLCO	Pemax	Pi max
Age	0.125	0.155	0.231	0.211	0.135	0.216
Height	0.246	0.299	0.172	0.284	0.244	0.189
Weight	0.144	0.184	0.177	0.271	0.156	0.183
Rheumatoid factor	0.344*	0.211	0.492*	0.497*	0.325*	0.399*
Disease duration	0.421*	0.176	0.467**	0.521**	0.430*	0.377*
ESR	0.288	0.212	0.351*	0.433*	0.388*	0.398*
MTX duration	0.219	0.281	0.254	0.322*	0.532*	0.421*

* $P < 0.05$

** $P < 0.01$

patients, but there was significant inverse correlation between lung function parameters and the rheumatoid factor titer, ESR, disease duration and methotrexate treatment duration ($P < 0.01$). Also, there was an inverse correlation between rheumatoid factor, ESR, disease duration, methotrexate duration and Pemax and Pimax (Table 9).

Discussion

JIA is the most common rheumatic disease in childhood with a very variable course. Cardiac involvement is common in JIA [9, 17], and it is the second major cause of mortality in this disease [18]. Ischemic heart diseases, hypertension and myocarditis are common causes of mortality; therefore, it is important to follow these patients through childhood.

In this study, JIA patients had no demonstrated cardiac symptoms; however, patients had significantly higher heart rate than in the control group but the absolute values within the normal limits. This increase in heart rate could be related to the inflammatory mediators' release of the disease. This is in agreement with the study of Bharti and his group [19], but Oguz et al. [9] found that the heart rate is non significantly increased. Also, our patients had significantly higher systolic and diastolic blood pressures when compared with control group even though the values were within the normal ranges, but such differences in childhood may lead to onset of overt hypertension as 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. Hypertension is an important cause of cardiac mortality in adults with RA. So, patients with JIA need close blood pressure monitoring and early onset hypertension can be detected and treated adequately [9, 19].

Pericarditis is one of the extra-articular manifestations of JIA and produces very mild or no symptoms, which resolve completely in most patients. The paucity of symptoms makes the clinical diagnosis of pericarditis very difficult; its incidence varies from 3 to 9% among patients with JIA. Necropsy studies, however, report a much higher incidence, ranging from 30 to 50% [20]. In this series of JIA patients, the pericardium was thickened with thin film of effusion in 6 (16.2%) patients. This is consistent with results of Ozer et al. [8] and Bernstein et al. [21], who reported the occurrence of pericarditis in 30 and 36%, respectively, of their series of JIA patients without any clinical evidence of pericarditis. In contrast to previous results, Oguz et al. [9], Bharti et al. [19] and Huppertz et al. [22] reported the absence of pericardial effusion in their JIA series.

Valvular involvement is a rare but serious complication of JIA. In our study, mitral valve is thickened with trace or mild regurge in 9 (24.3%) patients, while aorta is thickened only in 2 (5.4%) patients with no regurge. Our results are in accordance to Sircar et al. [23] who found 5 (10%) and 4

(8%) of their series of JIA showed mild mitral regurgitation and cusp thickening, respectively. Chen et al. [6] and Lee and Schueller [24] reported mitral and aortic affection in JIA patients. Also, Huppertz et al. [22] described four patients with aortic regurgitation out of 40 JIA patients. In contrast to our results, Oguz et al. [9] and Bharti et al. [19] did not mention valvular heart affection in their groups of JIA patients.

Regarding left ventricular systolic dimensions and function, our JIA patients had significantly enlarged diastolic LV and insignificantly reduced systolic function parameters (EF, FS) compared to controls but were within normal limits. These observations together with significantly higher resting heart rate compared to controls might represent a subclinical myocarditis. Our data are consistent with the data of Oguz et al. [9] and Bharti et al. [19]. Udayakumar et al. [25], in their study carried out on adult RA patients, found a significant increase in LVEDD, LVESD but with no significant difference in EF and FS. Gupta and Rao [26] stated that large left ventricular size and volume may be related to lower hemoglobin levels.

The serious deterioration in cardiac disease occurs in diastolic dysfunction. In this JIA series, diastolic dysfunction was appreciated in the form of reduced peak E velocity and increased peak A velocity, which is the reverse of normal and so, E/A ratio was significantly lower in the patients group. Other diastolic parameters such as Edt, Edur and Adt and IRT significantly prolonged, and E/F slope significantly decreased. Our study is in agreement with the studies of Oguz et al. [9] and Bharti et al. [19]. Huppertz et al. [22] 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. [27] 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.

This pervious pattern of diastolic dysfunction possibly reflects the increased LV filling during late atrial systole when compared to the early passive filling phase. This reflects an alteration in LV compliance and impaired diastolic relaxation [9, 19, 28].

In a comment by Gupta and Rao [26], it is 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 abnormalities could be due to a decrease in preload, an increase in after load or to impaired LV relaxation. The presence of increase of LV dimensions in our patients makes unlikely the possibility of decreased preload. Higher blood pressure and resting heart rate with consequent increased after load and reduced time available for myocardial relaxation, respectively, could contribute to the diastolic dysfunction. Also, it is partly due to an increase in myocardial fibrosis due to enhanced interstitial connective tissue deposition. Gupta and Rao [26] explained that the impaired relaxation of myocardium may be due to thickened and stiff pericardium, LV hypertrophy, interstitial fibrosis, ischemic changes (resulting in abnormal relaxation of the ventricle) and/or amyloid infiltration. Thus, the cause of abnormal diastolic parameters may be multiple and may be a cumulative effect of several factors. The diastolic dysfunction found in this study is usually seen in systemic hypertension, ischemic heart disease and cardiomyopathy. Our patients were completely asymptomatic, young and had no electrocardiographic abnormalities resembling ischemia. Such dysfunction might appear years before overt cardiac dysfunction becomes apparent.

In JIA, pulmonary complications are less frequent. Lung disease may precede the development of articular manifestation in systemic onset of JIA. Pleural effusion is the usual clinical manifestation, but parenchymal diseases such as interstitial pneumonitis, lymphocytic interstitial pneumonitis, bronchiolitis obliterans and rheumatoid nodules have been reported [29]. In our study, 4 (11.1%) patients out of 36 initially selected patients were unable to complete pulmonary functional evaluation. This could be due to extensive muscular and/or skeletal impairment [14] and difficulty for children in carrying out all maneuvers required in lung function tests. Camiciottoli et al. [14] also reported that 4 (13%) out of the 31 selected patients dropped from the study due to the same cause.

Pulmonary function abnormalities were found in 19 (59.3%) of completely asymptomatic patients group of whom 14 (43.7%) patients were restrictive and 5 (15.6%) patients were obstructive in pattern. This is consistent with data represented by Camiciottoli et al. [14] who found that 51.8% of their JIA series had pulmonary function abnormalities even in the absence of clinical and/or radiological evidence of pulmonary involvement. In contrast to our results, Noyes et al. [12] stated that the overall prevalence of pulmonary disease associated with JIA has been estimated to be 4–8% with more patients having pleural than parenchymal manifestations, and it is usually observed only in systemic onset disease.

In this study, FVC, FEV1, PEF and DLCO were significantly lower in diseased group (active and inactive) compared to controls. FEV1/FVC, RV and TCL were not different from controls. Furthermore, Pimax and Pemax were significantly lower in JIA patients compared with controls. Knook et al. [30] found that there was decrease in FVC, PEF, Pemax and Pimax, which were consistent with our results, but in contrast to ours, they found normal FEV1 and DLCO.

An impairment of thoracic and/or spine mobility has been suggested to reduce thorax excursion, resulting in a

tendency to develop lung function abnormalities [30–32]. But in our patients group, there was no impairment in thorax or spine mobility affecting lung function. A cycle of pain, stiffness and decreased activity lead to poor fitness and generalized muscle weakness [30, 33]. Impairment in respiratory muscle strength as measured by Pemax and Pimax could be a factor that influences lung function.

In our study, there was significant inverse correlation between ESR, disease duration and methotrexate treatment duration with lung function parameters and Pemax and Pimax. This might be explained with long-term MTX treatment, which is likely to be associated with severe active disease, high ESR, long disease duration, and therefore it is highly probable that this is associated with decreased respiratory muscle function. Also, the large number of patients still using MTX (57.18%), and some of them using prednisone (17.8%) imply that many of our JIA patients group had a history of severe disease activity associated abnormalities in lung function. Lung function was not related to age, height or weight of the patients.

MTX is the immunosuppressive drug most widely used in JIA. Regarding its known pulmonary toxicity has been reported since the late 1960s. Pelucchi et al. [34] concluded that the impairment of lung function in JIA is mostly related to the clinical subtypes of the disease instead of to MTX therapy. Another retrospective study showed that the side effects of MTX are mainly hepatic without alteration in respiratory diffusing capacity or development of restrictive pattern [35]. Schmelling et al. [36] postulated that with regard to lung function impairment, treatment with low-dose MTX appears to be safe even when performed for several years.

In conclusion, children with JIA are at risk for cardiac and pulmonary dysfunctions, regular cardiac and pulmonary appraisal as a part of the routine assessment of every patient with JIA may be one way to monitor these children.

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References

1. Hayward K, Wallace CA (2009) Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. Arthritis Res Ther 11:216. doi:10.1186/ar2619 BioMed Central Ltd
2. Classidy JT, Petty RE (2000) Textbook of pediatric rheumatology, 4th edn. W.B. Saunders, Philadelphia
3. Moore TL (1997) Juvenile rheumatoid arthritis. In: Rakel RE (ed) Conn's current therapy. W.B. Saunders, Philadelphia, pp 1001–1004
4. Barron KS (1990) Cardiovascular manifestations of connective tissue disease. In: Garson A, Bricker JT, McNamara DG (eds) The science and practice of pediatric cardiology. Lee and Febiger, Philadelphia
5. Goldenberg J, Ferraz MB, Pessoa AP, Fonseca AS, Carvalho AC, Hilario MO et al (1992) Symptomatic cardiac involvement in juvenile rheumatoid arthritis. Int J Cardiol 34:57–62
6. Chen YS, Yang YH, Lin YT, Chiang BL (2004) A patient diagnosed with pauciarticular juvenile rheumatoid arthritis after a mechanical prospective valve replacement due to aortic regurgitation. J Microbial Infect 37:200–202
7. Binstadt A, Levine C, Nigrovic A, Gauvreau K, Dedeoglu F, Fuhlbrigge C, Weindling N, Newburger W, Sundel P (2005) Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis. Pediatrics 116(1):e89–e93. doi:10.1542/peds.2004-2190)
8. Ozer S, Alehan D, Ozme S, Bakkaloglu A, Söylemezoglu O (1994) Mitral and aortic insufficiency in polyarticular juvenile rheumatoid arthritis. Pediatr Cardiol 15:151–153
9. Oguz D, Ocal B, Ertan Ü, Narin H, Karademir S, Senocak F (2000) Left ventricular diastolic functions in juvenile rheumatoid arthritis. Pediatric Cardiol 21:374–377
10. Kumar N, Rasheed K, Gallo R, Al-Hales Z, Duran CM (1995) Rheumatic involvement of all four heart valves: preoperative echocardiographic diagnosis and successful surgical management. Eur J Cardiothorac Surg 9:713–714
11. Cassidy JT (1992) Connective tissue diseases and amyloidosis. In: Oski FA, de Angelis C, Feigni RD, Warshaw JB (eds) Principles and practice of pediatrics. Philadelphia, J.B. Lippincott Co., pp 226–249
12. Noyes BE, Albers GM, deMello DE, Rubin BK, Moore TL (1997) Early onset of pulmonary parenchymal disease associated with juvenile rheumatoid arthritis. Pediatr Pulmonol 24:444–446
13. Rohayem J, Leupold W, Paul KD, Gahr M (2002) Pulmonary fibrosis and other clinical manifestations of small vessel vasculitis in a family with seropositive juvenile rheumatoid arthritis. Pediatr Pulmonol 33:65–70
14. Camiciottoli G, Trapani S, Castellani W, Ginanni R, Ermini M, Falcini F (1998) Effect on lung function of methotrexate and non-steroid anti-inflammatory drugs in children with juvenile rheumatoid arthritis. Rheumatol Int 18:11–16
15. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Godenberg J et al (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis. Second revision. Edmonton, 2001. J Rheumatol 31:390–392
16. Sahn DJ, DeMaria A, Kisslo J, Weyman A (1987) Recommendations regarding quantitaion in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 58:1072–1083
17. Nigrovic PA, White PH (2006) Care of the adult with juvenile rheumatoid arthritis. Arthritis Rheum (Arthritis Care Res) 55(2): 208–216. doi: 10.1002/art.21857© American College of Rheumatology
18. Hull RG (1988) Outcome in juvenile arthritis. Br J Rhrumatol 27:66–71
19. Bharti BB, Kumar S, Kapoor A, Agarwal A, Mishra R, Sinha N (2004) Assessment of left ventricular systolic and diastolic function in juvenile rheumatoid arthritis. J Postgrad Med 50(4):262–265
20. Goldenberg J, Pessoa AP, Roizenblatt S, Pavoa RMS, Hilario MO, Atra E, Ferraz MB (1990) Cardiac tamponade in juvenile chronic arthritis: report of two cases and review of publications. Ann Rheum Dis 49:549–553
21. Bernstein B, Takahashi M, Hanson V (1984) Cardiac involvement in juvenile rheumatoid arthritis. J Pediatr 85:313–317
22. Huppertz H, Voigt I, Muller-Scholden J, Sandhage K (2000) Cardiac manifestations in patients with HLA B27-associated juvenile arthritis. Pediatr Cardiol 21(2):141–147
23. Sircar D, Ghosh B, Ghosh A, Haldar S (2006) Juvenile idiopathic arthritis. Indian Pediatr 43(17):429–433

24. Lee SJ, Im HY, Schueller WC (2001) HLA-B27 positive juvenile arthritis with cardiac involvement preceding sacroiliac joint changes. Heart 86: e19 (http://www.heartjnl.com/cgi/content/full/86/6/e19)
25. Udayakumar N, Venkatesan S, Rajendiran C (2007) Diastolic function abnormalities in rheumatoid arthritis: relation with duration of disease. Singapore Med J 48(6):537–542
26. Gupta M, Rao PS (2004) Cardiac function in juvenile rheumatoid arthritis. Expert's comments. J Postgrad Med 50(4):266–267
27. Vlahos AP, Alfantaki S, Bechlioulis A, Vakalis K, Michalis LK, Siamopoulou A (2008) Early cardiovascular risk assessment in patients with juvenile idiopathic arthritis. Pediatric Rheumatol 6(1):S30. doi:10.1186/1546-0096-6-S1-S30
28. Appleton CP, Hatle LK, Popp RL (1988) Relation of transmitral flow velocity patterns to left ventricular diastolic function; new insight from a combined haemodynamic and Doppler echocardiographic study. J Am Cardiol 12:426–440
29. Rochat I, Sayegh Y, Gervaix A, Rimensberger PC, Argiroffo CB (2004) Acute hypoxic respiratory failure as the first manifestation of systemic-onset juvenile rheumatoid arthritis in a child. Pediatr Pulmonol 38:483–487
30. Knook LME, de Kleer IM, van der Ent CK, van der Net JJ, Prakken BJ, Kuis W (1999) Lung function abnormalities and respiratory muscle weakness in children with juvenile chronic arthritis. Eur Respir J 14:529–533
31. Cerveri I, Bruschi C, Ravelli A (1992) Pulmonary function in childhood connective tissue disease. Eur Respir J 5:733–738
32. Kearon C, Viviani GR, Kirkley A, Killian KJ (1993) Factors determining pulmonary function in adolescent idiopathicscolioses. Am Rev Respir Dis 148:288–294
33. Saag KG, Kolluri S, Koehnke M, Georgou TA et al (1996) Rheumatoid arthritis lung disease. Arthritis Rheum 39:1711–1719
34. Pelluchi A, Lomater C, Gerloni V, Foresi A, Fantini F, Marazzini L (1994) Lung function and diffusion capacity for carbon monoxide in patients with juvenile chronic arthritis: effect of disease activity and low dose methotrexate therapy. Clin Exp Rheumatol 12:675–679
35. Graharm LD, Myones BL, Rivas-Chacon RF, Pachman LM (1992) Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediatr 120:468–473
36. Schmeling H, Stephan V, Burdach S, Horneff G (2002) Pulmonary function in children with juvenile idiopathic arthritis and effects of methotrexate therapy. Journal Zeitschrift für Rheumatologie 61(2):168–172