Intensity of inflammation as the most important predictor of myocardial involvement in JIA. A 3D echocardiographic study.

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ACTA REUMATOL PORT. 2019;44:296-302

ABSTRACT

Introduction: Myocardial dysfunction is an important complication in the context of juvenile idiopathic arthritis (JIA). Several mechanisms might be involved in the induction of myocardial injury in such a disabling disease. Among several factors involved, myocardial inflammation and cardiotoxic drugs were thought to be the most incriminated factors. The aim of this work was to determine the most important factors that implicated myocardial injury in JIA and to weigh whether the severity of inflammation varies significantly among the several subtypes or not.

Methods: Sixty JIA patients as well as sixty, age and surface area, matched controls were subjected to conventional echocardiography, 3D Speckle tracking and the disease activity was measured as by Juvenile Arthritis Disease Score 27 (JADAS 27).

Results: JIA cases showed statistically significant systolic and diastolic dysfunction when compared to controls. Global longitudinal strain (GLS) (index of systolic function) was lower in cases compared to controls (JIA: 16.1±6.7 *vs* Controls: 23.9±1.4, P<0.0001), Left Ventricular ratio of early diastolic mitral inflow velocity to average of early diastolic velocities of the mitral annulus and basal septum (LV E/E') (index of diastolic function) was higher in cases compared to controls (JIA: 14.8±7 *vs.* Controls: 5.9±1.3, P<0.0001). There was no statistically significant difference in echocardiographic parameters as well as JADAS 27 between subtypes of JIA patients. Multivariate analysis showed that the best predictor of both systolic and diastolic involvement of the myocardium in JIA patients was the severity of inflammation rather than the duration or the type of medications used.

Conclusion: This study points out the potential of inflammation as an important inducer of myocardial injury in JIA. It also underlines the fact that this inflammation does not differ significantly according to the disease subtype.

Keywords: Juvenile idiopathic arthritis; Echocardiography.

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INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the commonest paediatric rheumatic disease with an estimated prevalence of 40 per 100000 in United Kingdom and 14 per 100000 children annually in United States of America[1].

JIA comprises a heterogeneous group of disorders with several subtypes according to ILAR classification: Oligoarticular (OA), Polyarticular (PA), both RF+/RF-, Systemic onset (SO), Enthesitis-related arthritis (ERA) and Psoriatic arthritis (PsA). There is increasing body of evidence pointing at cardiovascular involvement in JIA[2]. Chronic inflammation has been viewed as an important trigger of premature atherosclerosis with subsequent myocardial ischemia. Other predisposing factors for myocardial injury in such patients is the activation of cardiac fibroblasts with subsequent deposition of fibrous tissue that might impair myocardial relaxability[3].

Other theories of myocardial dysfunction include the deposition of amyloid tissue as a result of chronic inflammation and the stiffness of the surrounding pericardium leading to diastolic dysfunction and possibly systolic dysfunction due to subclinical channelopathies and involvement of coupling excitation cascade of myocardial fibers[4,5]. There is an estimate that 20% of deaths among JIA patients are related to myocardial damage varying from fulminant myocarditis to a commoner more insidious dysfunction with subsequent chronic

heart failure.[3]

The cornerstone in all mentioned mechanisms seems to be chronic inflammation. Thus the assessment of chronic inflammation is a very important factor in the prediction of myocardial involvement in JIA. Several scores are used for the assessment of disease activity in patients with JIA. The most widely used is the Juvenile Arthritis Disease Activity Score 27 (JADAS-27). Other measures such as Disease Activity Score 28 (DAS-28) are less commonly used in paediatrics. Moreover, several papers have proved that JADAS27 is more tailored to the paediatric subpopulation[2,6].

Despite several studies performed in the previous years about cardiovascular disorders in JIA patients, there are little if no answers on several substantial questions. The first of them is when to screen JIA patients with Echocardiography? Can JADAS score be used for screening to determine which patients are most susceptible to myocardial injury? Last but not least, does disease subtype or type of medications used impact severity of myocardial dysfunction? The goal of this study is to answer all the above three questions.

PATIENTS AND METHODS

STUDY SUBJECTS

This was a cross-sectional study conducted between December 2017 and December 2018. Sixty JIA patients aged between 6 and 18 years were recruited from Rheumatology Clinic of Cairo University Children Hospital according to the definition of the International League of Associations for Rheumatology (ILAR) classification.

Most of the patients were found to be within 3 subcategories which were oligoarthritis, polyarthritis and systemic-onset JIA. Meanwhile, patients with enthesitis-related arthritis or psoriatic arthritis were rarely observed at the Rheumatology clinic at the time allocated for our study. Therefore, they were not included in this study. Patients with congenital heart disease other than patent foramen ovale or other systemic diseases that can impair myocardial function were also excluded.

STUDY METHODS

Patients were subjected to a detailed history and examination for determination of disease onset, course and duration, medications used (from the onset of the disease until the time of the study) and JADAS 27 score. JADAS 27 was used to assess the disease activity and includes four measures: active joint count, physician's global assessment, parent's/patient's global assessment and recent laboratory reading of erythrocyte sedimentation rate (ESR).[8]

An echocardiography was performed for all patients and controls. Echocardiography was performed using General Electric (Vivid-N95, Horten, Norway) with Four Volume (4 V) having Tissue Doppler capabilities according to the guidelines of the American Society of Cardiology[9] as follows:

- Biplane (2D) derived EF (Simpson method): the LV endocardial border was manually traced contiguously from one side of the mitral annulus to the other side in 4,3 and 2 chambers view excluding the papillary muscles and trabeculations and the software provided the Ejection fraction automatically.
- Motion-Mode Echocardiography for determination of Fractional Shortening (FS)
- Conventional and Tissue Doppler Echocardiography for calculation of:
  - **Mitral E/A:** ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity.
  - **LV E/E'**: (Left Ventricular ratio of early diastolic mitral inflow velocity to average of early diastolic velocities of the mitral annulus and basal septum) as a potential measure of LV diastolic function[10].
- Three Dimensional (3D) Echocardiography: full-volume acquisition of the LV was obtained by harmonic imaging from the apical approach. Three ECG-gated consecutive beats were acquired during end-expiratory breath-hold to LV full volume. The depth and volume size were adjusted to obtain a temporal resolution higher than 30 volumes/s. All data sets were analyzed off-line using commercially available software (Tomtec). The software automatically identified the LV cavity endocardial border in 3D. The operator performed all the necessary adjustments manually in order to correctly place the endocardial border. Papillary muscles were included within the LV Chamber. After the adjustments software provided the LV volumes, Ejection Fraction, 3D Global Longitudinal Strain which is the mean of the longitudinal strain of all the 17 myocardial segments.

STATISTICAL ANALYSIS

Data were statistically described in terms of mean ± standard deviation (± SD), and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples when normally distributed and Mann Whitney *U* test for independent samples when not normally distributed. Echocardiographic data and JADAS 27 score were compared between the 3 main subtypes of JIA (OA, PA and SO) using one-way analysis of variance (ANOVA) with application of the Tukey-Kramer test for post-hoc pairwise comparisons if needed. We used multivariable linear regression modeling to identify determinants of average LV E/E' or LV GLS among the following medications used, disease duration, disease and JADAS 27 score. We tested the normality of distribution of continuous variables using the D'Agostino-Pearson test and by examination of the distribution plots (histograms and QQ plots). Since these variables showed marked positive skewness, we applied logarithmic transformation to the original values and entered the log-transformed values in the regression model. Nominal variables were entered as dummy variables. Finally, regression curves have been done to show the statistically significant relationship between LV GLS and LV E/E' on one hand and JADAS 27 on the other hand.

RESULTS

A total of sixty patients and sixty controls were included in our study, who were selected from the Rheumatology clinic of Cairo University Specialized Children's Hospital. The two groups were matched for age, sex and body surface area (BSA). Table I shows the comparison of demographic and clinical data of patients and controls. The mean age of JIA patients was 8.2 ± 3.3 years, while the control group mean age was 9.7 ± 4.4 years. Regarding the gender of the patients; most of them were females accounting for 67% of all patients. SOJIA patients were the largest group accounting for 47% of all participants while the Oligoarticular and Polyarticular groups accounted each for 26% of patients.

Table II shows that GLS was statistically lower in cases compared to controls (JIA: 16.1±6.7 vs Controls: 23.9±1.4, P<0.0001) and LV E/E' ratio (JIA: 14.8±7 vs. Controls: 5.9±1.3) was statistically higher in cases compared to controls.

Table III shows that Echocardiographic parameters and JADAS 27 were not different between subgroup of cases; apart from LV GLS, which was significantly higher in SOJIA compared to the other two disease subtypes.

Tables IV and V are two multivariate analyses

TABLE I. DEMOGRAPHIC AND CLINICAL DATA OF JIA CASES VS. CONTROLS

Variable	JIA (n=60)	Control (n=60)	P-value*
Age (years) (Mean±SD)	8.2 ± 3.3	9.7 ± 4.3	0.07
Height (cm) (Mean±SD)	118.8 ± 17.2	119.9 ± 17.5	0.6
Weight (kg) (Mean±SD)	22.9 ± 8.4	23.1 ± 16.3	0.7
BSA (m2) (Mean±SD)	0.85 ± 0.22	0.87 ± 0.32	0.6
Gender (M/F) (n/(%)66)	20(34%)/40(66%)	30(50%)/30(50%)	0.1
Classification			
Systemic Onset JIA (n/%)	29 (47.5)	–	–
Oligoarticular JIA (n/%)	16 (26.2)	–	–
Polyarthritis JIA (n/%)	15 (26.1)	–	–
Type of Treatment			
Steroids (n/%)	55 (91.8)	–	–
Methotrexate (n/%)	57 (95.1)	–	–
Biologic Agents (n/%)	25 (41%)	–	–
JADAS 27 (Mean±SD)	26.3 ± 15	–	–
Disease Duration (years) (Mean±SD)	4.13±0.9	–	–

BSA: Body Surface Area; cm: centimeter; F: Female; kg: Kilograms; JADAS: Juvenile Arthritis Disease Activity score; JIA: Juvenile Idiopathic Arthritis; m2: Square meter; M: Male; n: number; P: Pearson Value for statistical Significance; SD: Standard deviation.
P value <0.05 was considered statistically Significant

TABLE II. ECHOCARDIOGRAPHIC PARAMETERS IN JIA CASES VS. CONTROLS

JIA (n=60)	Controls (n=60)	Variable	P-value*
LVEDV (mL) (Mean±SD)	53.8±16.5	55.6±36.2	0.6
LV EF by MM (%)(Mean±SD)	77.5±8.1	76.2±6.5	0.5
LV EF by Simpson method (%) (Mean±SD)	73±2.3	71±1.6	0.7
LV FS (%) (Mean±SD)	45.7±7.9	44.2±3.6	0.3
Mitral E/A ratio (Mean±SD)	1.2±0.2	1.3±0.12	0.6
LV E/E' (Mean±SD)	14.8±7.0	5.9±1.3	<0.0001
LV GLS (%)) (Mean±SD)	16.1±6.7	23.9±1.4	<0.0001

EDV: End Diastolic volume; EF: Ejection Fraction; FS: Fractional Shortening; GLS: Global Longitudinal Strain; JIA: Juvenile Idiopathic arthritis; LV: Left Ventricular; LV E/E': Left Ventricular ratio of early diastolic mitral inflow velocity to average of early diastolic velocities of the mitral annulus and basal septum; Mitral E/A: ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity; mL: milliliter; MM: Motion Mode of echocardiography; n: number; P: Pearson Value of statistical Significance; SD: Standard Deviation. P value <0.05 was considered statistically Significant

TABLE III. JADAS 7 AND ECHOCARDIOGRAPHIC PARAMETERS IN SUBGROUPS OF JIA PATIENTS

	Type of JIA at onset			
	SOJIA (n=29)	OAJIA (n=16)	PAJIA (n=15)	P-Value
JADAS 27 (Mean±SD)	25±2	26±2	28±3	0.08
LVEDV (mL)(Mean±SD)	53.7±17.6	50.8±15.2	60.2±15.1	0.33
EF by MM (%)(Mean±SD)	75.8±7.5	80.7±6.5	75.6±11.3	0.08
LV EF by Simpson method (%) (Mean±SD)	72±1.6	73±1.2	72±1.8	0.8
FS (%)(Mean±SD)	44.2±7.5	48.6±6.4	44.3±10.3	0.11
Mitral E/A ratio (Mean±SD)	1.1±0.08	1.3±0.02	1.2±0.01	0.7
LV E/E'(Mean±SD)	14.26±6.71	15.33±7.37	15.30±7.38	0.84
LV GLS (%)(Mean±SD)	18.4±6.3	14.5±7.1	12.9±4.6	0.02

EDV: End Diastolic volume; EF: Ejection Fraction; FS: Fractional Shortening; GLS: Global Longitudinal Strain; JIA: Juvenile Idiopathic arthritis; LV: Left Ventricular; LV E/E': Left Ventricular ratio of early diastolic mitral inflow velocity to average of early diastolic velocities of the mitral annulus and basal septum; Mitral E/A: ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity; mL: milliliter; Mitral E/A: ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity; n: number; OA: Oligoarticular; P: Pearson Value of statistical Significance; PA: Polyarticular; SD: Standard Deviation; SO: Systemic Onset. P-value <0.05 was considered statistically significant.

showing that JADAS 27 is the only significant predictor of LV E/E' and GLS, respectively.

Figure 1 and 2 are 2 regression curves showing that JADAS 27 is well correlated with both LV E/E' (R2= 0.76) and GLS (R2=0.82), respectively.

DISCUSSION

The impact of chronic inflammation on the heart is the subject of many recent and old researches. There is increasing evidence that chronic inflammation, whether infectious or non- infectious, is a key-inducer of adverse myocardial remodeling[11].

JIA constitutes an important model for the study of the impact of chronic inflammation on the myocardium. However, important confounders such as the disease subtype and, more importantly, the drugs used in the treatment of JIA have been found.

In our series, statistically significant systolic and diastolic dysfunctions were depicted in JIA patients compared to controls. Such dysfunctions were only detectable by the new techniques of Echocardiography rather than the conventional M-Mode Echocardiography. The results mentioned are in agreement with previous series describing early diastolic and systolic dys-

TABLE IV. MULTIVARIABLE LINEAR REGRESSION MODEL FOR DETERMINANTS OF AVERAGE LV E/E'

	Unstandardized Coefficients		Standardized Coefficients			95% CI for B	
Independent variable	B	SE	Beta	t	P-value	Lower Bound	Upper Bound
Constant	0.160	0.132		1.215	0.230	-0.104	0.425
Log(JIA duration), years	-0.019	0.057	-0.028	-0.329	0.743	-0.132	0.095
PAJIA (=1)[a]	0.061	0.042	0.116	1.461	0.150	-0.023	0.146
OAJIA (=1)[a]	0.059	0.040	0.109	1.450	0.153	-0.023	0.140
Methotrexate (=1)[b]	-0.019	0.078	-0.018	-0.245	0.808	-0.175	0.137
Biological agents (=1)[c]	0.013	0.039	0.028	0.343	0.733	-0.064	0.090
Steroids (=1)[d]	-0.034	0.061	-0.040	-0.553	0.583	-0.155	0.088
Log(JADAS 27)	0.730	0.060	0.859	12.097	<0.001	0.609	0.851

Dependent variable is Log (Average LV E/E'). B: unstandardized regression coefficient; SE: standard error; Beta: standardized regression coefficient; t: t-statistic; 95% CI: 95% confidence interval; JADAS: Juvenile Arthritis Disease Activity Score; JIA: Juvenile Idiopathic Arthritis; OA: Oligoarticular; PA: Polyarticular.
a. Referenced to SOJIA (=0).
b. Referenced to 'No Methotrexate' (=0).
c. Referenced to 'No Biological Agents' (=0).
d. Referenced to 'No Steroids' (=0)

TABLE V. MULTIVARIATE ANALYSIS OF THE BEST PREDICTORS OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AS EXPRESSED BY LV GLS

	Coefficients	Standard Error	t Stat	P-value
Duration of JIA	0.096650009	0.120661	0.801006	0.426638
Methotrexate	2.580987532	1.440607	1.791597	0.078802
Biological agents	-0.760557673	0.646519	-1.17639	0.244599
Steroids	-0.680036459	1.077334	-0.63122	0.530559
JADAS 27	-0.311640702	0.019831	-15.7146	8.52E-22

EDV: End Diastolic volume; EF: Ejection Fraction; FS: Fractional Shortening; GLS: Global Longitudinal Strain; JIA: Juvenile Idiopathic arthritis; LV: Left Ventricular; LV E/E': Left Ventricular ratio of early diastolic mitral inflow velocity to average of early diastolic velocities of the mitral annulus and basal septum; Mitral E/A: ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity; mL: milliliter; MM: Motion Mode of echocardiography; n: number; P: Pearson Value of statistical Significance; SD: Standard Deviation. P value <0.05 was considered statistically Significant

functions in patients with JIA compared to their age-matched controls[12].

Our series also show failure of JADAS 27 score to discriminate between the three subtypes of JIA. No statistically significant difference was depicted between the three disease subtypes' patients as regards the JADAS 27 score. This proves that the severity of inflammation is not characteristic of a subtype over another and goes in agreement with the Vakili *et al.* series, which showed the same findings using platelet indices as a marker of inflammation in JIA[13].

Kulh *et al.* hypothesize that persistent viral infection is the basis of development of both progressive systolic and diastolic dysfunctions in cases with dilated cardiomyopathy. Moreover, Kusisto *et al.* showed an abnormal myocardial viral load in cases with hypertrophic cardiomyopathy[14,15].

Non-infectious inflammatory disorders such as Systemic Lupus Erythematosus as well as JIA have been all reported to induce myocardial remodeling as a result of chronic inflammation[16].

In our series the best predictor of both systolic and diastolic dysfunction was the JADAS 27 score. The latter has been declared as an important predictor of

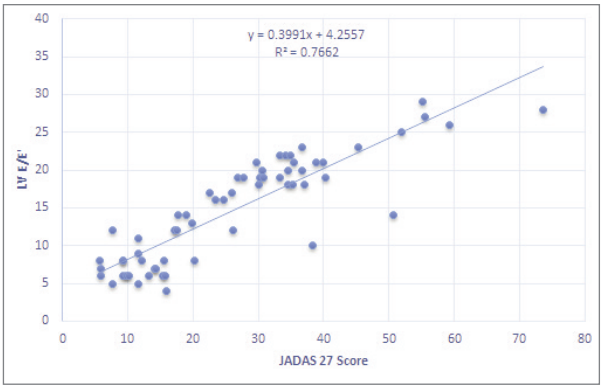

FIGURE 1. Regression curve showing that JADAS 27 is well correlated with LV E/E' (R2=0.76) and GLS (R2=0.82)

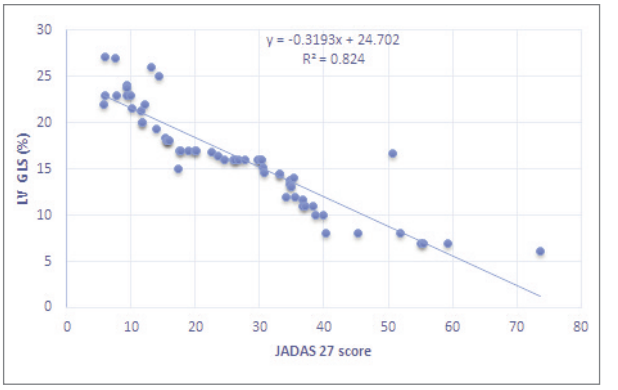

FIGURE 2. Regression curve showing that JADAS 27 is well correlated with GLS (R2=0.82)

disease activity and level of inflammation in different subtypes of JIA. Disease duration, disease subtype as well as type of medications used failed to show any statistically significant correlation with LV E/E' and LV GLS.[6]

The aforementioned findings underline the importance of chronic inflammation in the induction of myocardial injury in JIA patients. The degree of inflammation as measured by JADAS might impair myocardial function whatever the disease duration is and does not seem to be characteristic of a particular type despite the common cliché which claims a more severe inflammation in Systemic Onset JIA (SOJIA).

CONCLUSION

This study represents a continuum of previous ones underlying the myocardial involvement in JIA and it unleashes some new facts such as the importance of the severity of inflammation as measured by JADAS 27 as a core inducer for myocardial involvement. It also underlines the fact that neither the severity of inflammation nor myocardial function impairment are related to a certain subtype of the disease over the other. This might indicate that JADAS 27 can be used as a stratifying factor to indicate whether to screen patients with JIA for myocardial dysfunction or not.

ACKNOWLEDGMENT

We recently created an initiative termed "Research Accessibility Team" to allow the extensive participation of medical students and interns in research. We want to thank all the passionate students who are partnering with us and we believe that their very deep passion is driving us to create and work hardly so as not to let them down.

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