Assessment of Left Ventricular Function by Tissue Doppler, Strain and Strain Rate Echocardiography in Children with Juvenile Idiopathic Arthritis: An Observational Study

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Introduction
Juvenile idiopathic arthritis (JIA), a chronic, systemic, inflammatory disease affecting the synovial tissues and whose origin has not been entirely elucidated, is the most frequent cause of chronic arthritis in childhood. It can also manifest itself as a chronic disease that affects various organs and systems, with a preponderance of joint findings. Cardiac involvement in JIA is generally silent, although life-threatening complications may be seen. Echocardiography is an established investigation to evaluate cardiovascular involvement . Classic echocardiographic methods have been used until now to evaluate left ventricular function in children with JIA. Tissue Doppler echocardiography (TDE) can help evaluate local myocardial segments and calculate myocardial function. "Strain" and "strain rate" (SR) measurements, derived from tissue Doppler myocardial imaging technique, were developed as a new method to measure the percentage and speed of regional deformation. We therefore aimed to evaluate left ventricular segmental systolic and diastolic function by the tissue Doppler imaging method in JIA patients who presented no cardiovascular symptoms and had normal findings by standard echocardiography.

Methods

Study Population
Thirty children with JIA were included in this study. They had been followed up from February 2010 to March 2011 at the Pediatric Nephrology Clinic of the Dr. Sami Ulus Gynecologic, Obstetrical and Pediatric Disease Teaching and Research Hospital and diagnosed with JIA (polyarticular type) according to the International League against Rheumatism (ILAR) classification criteria. These patients had also been referred to the Pediatric Cardiology Department for cardiac evaluation and found free of heart failure, arrhythmia (atrioventricular block or branch block), pericarditis or chronic heart disease.

Essential Clinical Characteristics
The patients' age, sex, weight, heart rate, mean blood pressure, disease duration, and current corticosteroid and disease-modifying drug (DMARD) use were recorded. Hemoglobin (Hgb), WBC, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were determined; telecardiography and electrocardiography (EKG) were performed. In addition to conventional echocardiography, all patients also underwent a left ventricular function evaluation by tissue Doppler, strain and SR techniques. The control group consisted of 30 healthy children without heart problem, who had been referred to the Pediatric Cardiology Division for evaluation of a cardiac murmur, selected to match the sex and age distribution of the JIA patients.
Ethical Committee approval for the study was obtained from the Ankara University Medical School. Signed Informed Consent forms were obtained for the study participants.

Echocardiography
Measurements were made by pulse-wave TDE and strain/SR echocardiography in both JIA patients and control group subjects. Echocardiographic recordings were made of the subjects in the supine and/or left lateral decubitus position by a pediatric cardiologist, using a 3 MHz probe on a Vivid 7 device (GE Medical Systems, Norway) simultaneously with a DII derivation EKG monitoring. The left ventricular function parameters for both study patients and control group were evaluated by TDE and strain/SR echocardiography.

Tissue Doppler Imaging
The TDE records considered those in which the best quality image and the highest amplitude had been acquired for each patient. After activating the Tissue Doppler mode on the device, apical 4-chamber and 2-chamber views were obtained. The Nyquist limit was set in the interval between -20 and +20 cm/sec, and the frame rate to "high" (>100 frames.s^{-1}). In the apical 4-chamber view, the tissue Doppler sampling volume was set to the following segments: free wall of the left ventricle basal, middle and apical; septal basal, middle and apical, and these six sets of regional TDE data were assessed. The systolic and diastolic waves representing myocardial motion were imaged. Peak velocities of the positive S'-wave, arising during ventricular systole, negative E'-wave produced in the early diastolic filling phase and the negative A'-wave resulting from the late diastolic left atrial contraction were measured in the cardiac cycle. Isovolumic relaxation time (IRT), isovolumic contraction time (ICT) and myocardial performance index (MPI) were derived with the help of these wave measurements.

Strain/Strain Rate Imaging
Strain and SR data were obtained in real-time SR imaging mode, with the help of the patients' 4-cavity and short axis echocardiographic images. Digitally recorded data of at least three consecutive beats were analyzed post-process with the software included in the device (EchoPac 6.3.6, Vingmed, General Electric). Longitudinal, radial and circumferential SR and strain profiles were obtained from specific myocardial segment images.

Statistical Evaluation
The Statistical Package for Social Sciences for Windows 11.5 (SPSS, SPSS Inc, Chicago, IL, USA) was used for statistical evaluation. Descriptive statistics were expressed as mean ± 1 standard deviation (SD), with percentages (%) for categorical variables. The Kolmogorov-Smirnov test was used for fitness of sample values to normal distribution. The group values were compared by Student's t-test if normally distributed, and by the Mann-Whitney U test if not. Correlations among variables were evaluated by Pearson's test. All quantitative results were expressed with their 95% confidence limits; a p-value <0.05 was accepted as significant.

General Findings
Of the 30 JIA patients, 13 (44%) were male and 17 (56%) female; they were aged 4-19 (mean 11.3±3.9 years). As for the control group, it consisted of 14 (47%) boys and 16 girls, aged 4-18 (mean 10.8±3.6 years). In the study patients group, all patients had polyarticular type JIA. Of these, 11 (36.6%) had active disease and 19 (63.4%) were in remission. The mean activity score of the patients in the study group was 2.8, and the average number of involved joints was one. Rheumatoid factor was positive in two patients only. There was no significant difference between the study patients and the control group as to their average heart rate and their Hgb or WBC levels (p>0.05). There was no statistically significant difference (p>0.05) either in the left ventricular ejection fraction (EF) or the shortening fraction (SF) between these two groups (Table 1). A correlation could not be established between the strain and SR echographic parameters and the duration of corticosteroid or DMARD treatment (p>0.05). Mid-septal, apical-septal, apical-lateral and mid-lateral longitudinal SR Peak E parameters were found to correlate significantly with the duration of disease.

Correlation Test Results
There was a significant correlation in the patient group between the duration of disease on one the hand with left ventricular global strain, and longitudinal basal-septal, mid-septal and apical-lateral strain peak S values on the other (p<0.05, r respectively 0.354, 0.42, 0.41 and 0.42).

Tissue Doppler Findings
Among left ventricular tissue Doppler values, E' values obtained from the mid-lateral and apical-lateral segments were significantly higher in the patients with comparison to those of the control group (p<0.05). There was no significant difference among the different segments as to A', E'/A', MPI and IRT values.

Strain Findings
Left ventricular strain echocardiography parameters for the study patient and control groups are shown in Table 3. The difference in the left ventricular global strain value between the study patient and control groups was significant (p<0.05). Basal-septal, mid-septal and apical-lateral longitudinal S, and lateral circumferential S values were significantly lower in the JIA patients than in the control group (p<0.05).

Strain Rate Findings
Table 4 shows the left ventricular longitudinal, radial and circumferential SR peak S, A and E values. The left ventricular apical-lateral longitudinal SR peak S value, mid-septal and apical-septal lateral longitudinal SR peak E values, The left ventricular circumferential SR peak S value in the anterior, posterior and inferior segments, and the left ventricular lateral and posterior circumferential SR peak E values were all significantly lower in the study patients as compared to the control group (p<0.05 for all).

Table 1. Age, weight, left ventricular function parameters, clinical and laboratory characteristics of the JIA patient group and the healthy control group

	Patients Mean ± 1 SD	Controls	p* (statistical significance)
Age	11.30±3.99	10.86±36	0.94
Dis. duration, years	4.12±2.44	-	
CS dur., mo.	34.76±25.12	-	
DMARD dur., mo.	32.80±25.19	-	
HR, bpm	98.74±17.66	95.50±15.22	0.83
BP mean, mmHg	79.52±15.18	86.62±8.12	0.024
ESR, mm/s	23.64±19.42	3.44±4.59	0.001
CRP, mg/L	14.80±25.15	9.46±3.42	0.001
Hgb, g/dL	12.001±28	12.01±0.72	0.53
WBC /mm^3	9.85±3.52x10^3	8.66±2.49x10^3	0.24
LVEF, %	71.72±7,76	73.42±5.21	0.17
SR, %	42.76±5.95	43.78±6.54	0.22
Body weight, Kg	34.14±15.15	36.64±12.80	0.38
Height, cm	133.03±20.74	135.71±15.99	0.77

(CRP: C-reactive protein; DMARD dur.: Disease-modifying drug treatment duration; ESR: Erythrocyte sedimentation rate, Hgb: Hemoglobin; CS dur.: Corticosteroid treatment duration; BP: Arterial blood pressure; SD: Standard deviation)
Data expressed as mean±1 SD
* by Student's t-test

Table 2. Left ventricular tissue Doppler parameters of JIA patients and healthy controls

LV lateral wall	Patients Mean±1 SD	Controls Mean±1 SD	p*	LV septum	Patients Mean±1 SD	Controls Mean±1 SD	p*
Basal E', cm/s	17.43±3.70	19.21±3.60	0.07	Basal E', cm/s	14.32±2.46	15.49±1.99	0.07
Basal A', cm/s	6.90±1.52	7.12±1.40	0.56	Basal A', cm/s	6.23±1.44	6.55±1.19	0.28
Bazal E'/A'	2.01±0.78	2.71±0.55	0.52	Basal E'/A'	2.49±0.55	2.49±0.55	0.79
Basal IRT, ms	49.81±7.64	53.64±10.81	0.14	Basal IRT, ms	50.60±6.02	50.48±7.58	0.95
Basal MPI	0.370±0.10	0.381±0.11	0.66	Basal MPI	0.360±0.11	0.350±0.11	0.83
Mid E', cm/s	15.76±3.24	17.91±3.29	0.011	Mid E', cm/s	12.56±2.50	13.00±1.73	0.40
Mid A', cm/s	5.73±1.144	6.36±1.244	0.051	Mid A', cm/s	4.91±1.27	5.46±0.82	0.07
Mid E'/A'	2.82±0.64	2.87±0.44	0.63	Mid E'/A'	2.66±0.65	2.44±0.51	0.56
Mid IRT, ms	52.90±9.14	52.89±7.38	0.67	Mid IRT, ms	48.12±7.72	48.22±6.34	0.95
Mid MPI	0.385±0.15	0.377±0.10	0.66	Mid MPI	0.35±0.15	0.36±0.10	0.17
Apical E', cm/s	11.10±2.96	12.64± 2.42	0,043	Apical E', cm/s	9.05±2.14	10.23±2.37	0.07
Apical A', cm/s	4.88±0.98	5.29±1.18	0.14	Apical A', cm/s	4.14±0.75	4.55±0.933	0.11
Apical E'/A'	2.30±0.67	2.47±0.64	0.61	Apical E'/A'	2.25±0.69	2.34±0.45	0.63
Apical IRT, ms	51.10±8.84	52.40±7.64	0.43	Apical IRT, ms	48.19±7.46	45.37±73	0.14
Apical MPI	0.38±0.18	0.38±0.18	0.55	Apical MPI	0.35±0,16	0.34±0.07	0.52

(A': late diastolic velocity; E': early diastolic velocity; IRT: Isovolumic relaxation time; LV: left ventricle; MPI: Myocardial performance index; ms: millisecond; s: second; SD: standard deviation)
Data expressed as mean±1 SD
* Mann-Whitney U test

Table 3. Left ventricular strain parameters for the JIA patient and control groups.

	Patients	Controls	
	Mean±1 SD	Mean±1 SD	p*
LS basal septal peak S	-18.23±4.62	-21.53±2.69	0.002
LS mid-septal peak S	-20.35±3.75	-22.75±3.50	0.002
LS apical septal peak S	-20.47±6.96	-24.11±4.26	0.062
LS apical lateral peak S	-17.30±6.22	-21.97±4,32	0.002
LS mid-lateral peak S	-13.97±5.76	-17.17±4.18	0.067
LS basal-lateral peak S	-13.49±7.99	-14.28±5,56	0.779
RS anter.-sept. peak S	29.85±17.25	28.11±18.68	0.49
RS lateral peak S	36.49±38.26	27.56±17.96	0.54
RS lateral peak S	31.67±19.20	28.11±17.61	0.54
RS posterior peak S	33.57±18.96	29.57±18.95	0.33
RS inferior peak S	33.51±18.23	30.27±20.71	0.27
RS septal peak S	31.12±15.48	29.87±18.6	0.44
CS anterior septal S	-25.32±6.57	-23.16±8.44	0.33
CS anterior peak S	-17.61±5.15	-19.72±6.35	0.17
CS lateral peak S	-9.68±7.12	-13.70±6.81	0.02
CS posterior peak S	-7.59±5.87	-9.23±7.58	0.08
CS inferior peak S	-17.60±23.24	-12.12±8.95	0.77
CS septal peak S	-24.83±6.37	-22.39±9.52	0.47
Global strain	-17.05±2.97	-20.09±2.91	0.00

(LS: Longitudinal strain, RS: Radial strain, SD : standard deviation CS: Circumferential strain,)
Data expressed as mean±1 SD
* Mann-Whitney U test

Table 4. Left ventricular longitudinal, radial and circumferential SR peak S, A and E values for JIA patient and control groups.

	Patients / Controls Mean±1 SD		p*
LS basal septal peak S	-1.30±0.33	-1.48±0.42	0.08
LSR mid-septal peak S	-1.39±0.39	-1.51±0.34	0.22
LSR apical septal peak S	-1.55±0.71	-1.69±0.53	0.14
LSR apical lateral peak S	-1.44±0.66	-1.74±0.97	**0.02**
LSR mid-lateral peak S	-1.24±0.46	-1.24±0.57	0.06
LSR basal-lateral peak S	-1.87±0.77	-1.69±0.41	0.54
LSR basal septal peak E	1.79±0.67	2.03±0.69	0.11
LSR mid-septal peak E	1.99±0.64	2.47±0.57	**0.001**
LSR apical septal peak E	2.51±0.76	3.31±0.87	**0.001**
LSR apical lateral peak E	2.22±1.00	3.17±0.87	**0.000**
LSR mid-lateral peak E	1.62±0.84	2.15±0.72	**0.005**
LSR basal-lateral peak E	2.14±0.93	1.87±0.76	0.27
LSR basal septal peak A	1.22±0.81	1.35±0.89	0.33
LSR mid-septal peak A	1.15±0,88	1.30±0.78	0.20
LSR apical septal peak A	1.00±0.90	1.03±0.78	0.35
LSR apical lateral peak A	1.16±1.12	1.29±0.70	0.20
LSR mid-lateral peak A	0.93±0.86	1.10±0.31	0.39
LSR basal-lateral peak A	1.37±0.76	1.16±0.61	0.26
RSR septal peak S	1.65±0.52	1.85±0.70	0.27
RSR anterior peak S	1.79±0.56	1.86±0.69	0.84
RSR lateral peak S	1.87±0.66	1.90±0.61	0.75
RSR posterior peak S	1.87±0.69	1.94±0.66	0.56
RSR inferior peak S	1.81±0.66	1.94±0,.73	0.33
RSR septal peak S	1.59±0.61	1.69±0.76	0.22
RSR anterior septal peak E	-1.63±0.77	1.79±1.10	0.90
RSR anterior peak E	-1.63±0.82	-1.91±1.17	0.53
RSR lateral peak E	-1.71±0.80	-1.93±1.18	0.62
RSR posterior peak E	-1.75±0.95	-1.95±1.25	0.84
RSR inferior peak E	-1.65±1.15	-1.75±1.15	0.57
RSR septal peak E	-1.56±1.26	-1.65±1.00	0.46
RSR anterior septal peak A	-1.15±0.89	-1.07±0.71	0.99
RSR anterior peak A	-0.93±1.15	-1.16±0.78	0.39
RSR lateral peak A	-1.22±0.86	-1.14±0.73	0.73
RSR posterior peak A	-1.15±0.73	-1.13±0.59	0.83
RSR inferior peak A	-1.19±0.69	-1.24±0.80	0.91
RSR septal peak A	-1.21±0.75	-1.18±0.73	0.90
CSR anterior septal peak S	-1.79±0.69	-1.80±0.70	0.64
CSR anterior peak S	-1.26±1.01	-1.65±0.69	**0.036**
CSR lateral peak S	-1.21±0.41	-1.41±0.61	0.09
CSR posterior peak S	-0.96±0.37	-1.25±0.66	**0.008**
CSR inferior peak S	-1.25±048	-1.47±0.73	**0.043**
CSR septal peak S	-1.81±0.66	-1.8±0.7	0.73
CSR anterior septal peak E	2.93±0.67	2.81±0,62	0.39
CSR anterior peak E	2.27±0.96	2.05±.90	0.41
CSR lateral peak E	1.32±0.83	1.88±0.94	**0.007**
CSR posterior peak E	1.31±0.71	1.85±0.91	**0.028**
CSR inferior peak E	1.71±0.71	1.85±0.81	0.37
CSR septal peak E	2.59±0.56	2.52±0,70	0.72
CSR anterior septal peak A	1.59±1.06	1.20±0,52	0.77
CSR anterior peak A	1.27±0,84	1.10±0.49	0.97
CSR lateral peak A	0.82±0.77	0.88±0.50	0.33
CSR posterior peak A	0.64±0.55	0.88±0.80	0.22
CSR inferior peak A	0.86±0.55	1.02±0.75	0.41
CSR septal peak A	1.34±0.93	1.28±0.71	0.46

(LSR: Longitudinal strain rate, RSR: Radial strain rate, SD : standard deviation CSR: Circumferential strain rate)
Data expressed as mean±1 SD
* Mann-Whitney U test

Limitations of the Study
This study derives its importance from being the first study of regional myocardial function in children with JIA. We have shown regional myocardial changes in the left ventricle of JIA patients. The first limitation is the fact that the angle at which the transducer was held with respect to the target myocardial tissue by the same investigator may modify TDE, strain and SR results. The small patient and control subject numbers and short follow-up duration are a second limitation, while a third is that the study population was comprised of only patients with the polyarticular type of the disease, rather than having different other types represented.

Conclusion
We have observed that myocardial involvement that cannot be established by a tissue Doppler investigation aimed at determining early changes in regional systolic and diastolic function, due to subclinical cardiac disease in JIA, may be observed thanks to strain and SR echocardiography. We would like to stress the remaining need for multiple studies in larger numbers of patients.