# Cardiac Function in Adult Patients with Juvenile Idiopathic Arthritis

Hanne A. Aulie, Mette E. Estensen, Anne M. Selvaag, Vibke Lilleby, Klaus Murbraech, Berit Flatø, and Svend Aakhus

***ABSTRACT.*** ***Objective.*** To compare cardiac function in adults with longterm juvenile idiopathic arthritis (JIA) with that of healthy controls, and to investigate the influence of inflammation, disease severity, and use of antirheumatic medication on cardiac function.

***Methods.*** Eighty-five patients with JIA (median age 38.6 yrs) with active disease for at least 15 years were reexamined at a median of 29 years after disease onset and compared with 46 matched controls. Echocardiography, including tissue Doppler imaging and longitudinal peak-systolic global strain, was used to assess diastolic and systolic myocardial function, and 12-channel electrocardiography was performed.

***Results.*** The interventricular septum was thicker in patients than controls (mean ± SD 0.8 ± 0.2 cm vs 0.7 ± 0.1 cm, p = 0.036). Diastolic function in patients was altered compared with controls characterized by lower mitral E wave deceleration time (165 ± 36 ms vs 180 ± 40 ms, p = 0.029), higher surrogate marker of left ventricular (LV) filling pressure (median lateral E/e' 5.3, interquartile range 4.6–6.3 vs 4.8, 3.9–5.7, p = 0.036), and larger left atrial area (16.4 ± 2.9 $cm^2$ vs 15.1 ± 2.8 $cm^2$, p = 0.015). Systolic and diastolic blood pressures were higher in patients (120 ± 15 mmHg vs 114 ± 9 mmHg, p = 0.021 and 76 ± 10 mmHg vs 71 ± 8 mmHg, p = 0.009, respectively). QT corrected interval was similar in patients and controls. High high-sensitivity C-reactive protein (CRP), polyarticular disease course, and extended joint affection at 29-year followup, as well as duration of active disease, cumulative erythrocyte sedimentation rate, and CRP, and prednisolone use were associated with higher lateral E/e'.

***Conclusion.*** Adult patients with JIA did not differ from controls in LV systolic function, but had mildly thicker interventricular septum and indications for higher LV filling pressure, and most in patients with a higher disease burden. (First Release July 15 2015; J Rheumatol 2015;42:1716–23; doi:10.3899/jrheum.141351)

*Key Indexing Terms:*
JUVENILE IDIOPATHIC ARTHRITIS
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Juvenile idiopathic arthritis (JIA) is a chronic inflammatory rheumatic disease that is diagnosed in childhood and has an annual incidence of about 15 cases per 100,000 children[1,2]. About 50% of the patients have active disease when they reach adulthood[3,4,5]. We have recently reported that 41% of the patients in the present cohort had active disease or used antirheumatic medication 30 years after disease onset[6].

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Patients with adult-onset rheumatoid arthritis (RA) have an increased risk of congestive heart failure and a higher prevalence of diastolic dysfunction compared with individuals without RA[7,8,9]. Recently, an association between inflammation and a prolonged corrected QT interval (QTc) was found in patients with RA, and a higher QTc was correlated with all-cause mortality[10].

While we previously have reported an increased prevalence of hypertension (HTN) and altered arterial properties in adults with longstanding JIA[11], cardiac function in adults with longstanding JIA has not been assessed, to the best of our knowledge.

Tissue Doppler imaging (TDI) by echocardiography enables the evaluation of both systolic and diastolic myocardial function in addition to the traditional variables such as ejection fraction (EF) and mitral flow velocities[12,13]. The longitudinal peak-systolic global strain derived from 2-dimensional speckle tracking analysis provides additional information on regional and global myocardial function[14].

The aims of the present study were to compare the cardiac function in adult patients with JIA with longterm active disease to that of age- and sex-matched controls and to assess

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whether a larger inflammatory burden, more severe disease, or the use of antirheumatic medication had an adverse effect on cardiac function.

## MATERIALS AND METHODS

*Patients and controls*. The cohort of 254 patients from which the 85 included patients were selected has previously been described in detail[3,6,15,16]. Comprehensive information about the selection criteria for our study has been presented[11]. Briefly, the patients were initially referred to the Oslo University Hospital (OUH) between 1980 and 1985. Subsequently, they were examined clinically after a median of 15 years of disease duration and by a mailed questionnaire after a median of 23 years. The 134 patients with clinically active disease at the 15-year, 23-year, and/or 29-year followups were invited to participate in the present study. Ninety patients consented (67%) and were enrolled in the study between May 2011 and March 2012 (29-yr followup). Five patients were excluded after inclusion because of pregnancy (n = 3), technical complications (n = 1), or severe heart disease without relation to JIA (n = 1). Retrospective analyses of the data from the 134 eligible patients at the 15-year followup did not demonstrate any differences concerning sex, disease duration, or variables of disease activity and severity between the 85 patients included and the 49 eligible but not participating patients (data not shown). However, the participants were a median of 5.1 years older than the nonparticipants.

Forty-six healthy controls matched for age and sex were randomly selected from the Norwegian population register. Responders were not allowed into the control group if they had a history of diabetes mellitus, HTN, previous cardiovascular (CV) events, or inflammatory arthritis.

This study was approved by the Regional Ethics Committee for Medical Research, and written informed consent according to the Declaration of Helsinki (2008) was obtained from all the participants.

*Clinical examination and CV risk assessment*. A specialist in rheumatology (BF, AMS, or VL) performed a clinical examination of the 85 patients, including the 71 joint count, the physician's global assessment of disease activity (10-cm visual analog scale), and general organ status. The International League of Associations for Rheumatology classification criteria were used to classify JIA[17]. Active disease was defined as the lack of remission while not taking antirheumatic medication[18]. For the subgroup analyses, the patients who had cumulative involvement of more than 4 joints during their disease course were included in the polyarticular course type, and the patients with involvement of 4 joints or fewer were included in the oligoarticular course type. The controls were clinically examined by 1 investigator (HAA).

Information regarding comorbidities and a family history of premature CV disease (CVD), which was defined as a first-degree relative having CVD before the age of 65 years in women and 55 years in men, were obtained by interviewing the participants. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after a 5-min rest in a supine position. Three measurements with a difference of < 5 mmHg were averaged. The presence of arterial HTN was defined as SBP > 140, DBP > 90 mmHg, and/or the use of antihypertensive medication. Waist circumference was measured and body mass index was calculated in all the participants.

*Echocardiography*. We performed a standard transthoracic echocardiographic examination of the patients and controls using a Vivid 7 or E9 ultrasound scanner (GE Vingmed Ultrasound) as recommended[19]. All the recordings were measured after at least a 5-min rest, and 3 consecutive heart cycles were stored for offline analyses in dedicated software EchoPAC vs 1.1.12 (GE Vingmed Ultrasound). Pulse-wave Doppler with the sample volume at the aortic annulus and the tip of mitral leaflets (apical position) was used to obtain the blood flow velocity in the left ventricular (LV) outflow tract and mitral inflow, respectively. The LV dimensions were measured after convention from parasternal M-mode registrations[20]. The left atrial (LA) area was obtained from the 4-chamber view. Pulse-wave Doppler was used to measure early (E) and late (A) transmitral diastolic flow velocities (Appendix 1) from which the transmitral E/A ratio was calculated. The E wave deceleration time (DT) and the isovolumic relaxation time (IVRT) were recorded[21]. The LV mitral annular velocities in systole (LV s') and early diastole (LV e') were measured in the septal and lateral mitral annulus with color TDI (Appendix 1). The E/e' ratio, a surrogate marker of LV filling pressure, was calculated[22]. The LV end-diastolic volume and EF were measured by Simpson modified biplane rule[20]. The global longitudinal myocardial strain was measured to obtain regional and global myocardial function[14].

All the echocardiographic recordings and analyses were performed by 1 investigator (HAA) at the echocardiographic laboratory of OUH Rikshospitalet. The offline data re-analyses were blinded for clinical information and patient/control identity. All the variables were averaged from 3 heart cycles, except for the global longitudinal strain, which was derived from the analyses of single-beat recordings of 3 apical image projections. Intraobserver reproducibility of echocardiographic variables was assessed by 1 observer's analysis of 2 independent echocardiograms from 25 consecutive patients. Reproducibility was assessed in our laboratory by a technician's repeat analysis of echocardiograms with > 2 weeks' interval, expressed as the coefficient of repeatability (CR; i.e., 1.96× SD of difference between observers)[23].

*Electrocardiography (ECG)*. The patients and controls underwent a standard 12-channel ECG recording. The ECG recordings were reviewed for abnormalities, such as QTc prolongation, bundle branch blockage, T wave abnormalities, and chamber enlargement by a reader blinded for patient/control identity. The rhythm, PR interval, QRS duration, and QTc interval were registered.

*Questionnaire*. A questionnaire including data on smoking habits and physical activity was completed by all the participants. The total work and leisure time physical activity of vigorous and moderate intensities were measured by the short International Physical Activity Questionnaire[24,25].

*Laboratory assessments*. Blood samples were collected after an overnight fast in the patients and controls and were analyzed for total cholesterol, triglycerides, high-sensitivity CRP (hsCRP), glucose, glycosylated hemoglobin (HbA1c), and prohormone of brain natriuretic peptide. One patient with JIA had Type 2 diabetes and was excluded from the analyses concerning glucose and HbA1c. The erythrocyte sedimentation rate (ESR) area under the curve (AUC) was calculated from variables measured at disease onset and 15- and 29-year followups. The CRP AUC was calculated from the variables assessed at the 15- and 29-year followups.

*Statistics*. The differences between the patients with JIA and matched controls and between the 2 patients groups were tested by an independent sample Student t test for the continuous normally distributed variables, the Mann-Whitney U test for the continuous not normally distributed values, and the chi-square test for the categorical variables. Central tendencies were presented as the mean ± SD for the continuous normally distributed variables, and as the median and interquartile range for the continuous not normally distributed values.

Spearman correlation was used to investigate the association between cumulative inflammatory burdens, years on prednisolone, and lateral E/e' at the 29-year followup. To identify the predictors of lateral E/e', the candidate factors associated with lateral E/e' in Spearman correlation analysis ($p < 0.05$) and age and sex were tested in a subsequent multivariate analysis with the backward deletion of possible determinants. The p values < 0.05 (2-tailed) were regarded as statistically significant for all the analyses. SPSS Version 20 (SPSS) was used for the statistical analyses.

## RESULTS

*Demographics and CV risk factors*. The patient characteristics are summarized in Table 1. HTN was present in 11% of the patients, and the SBP and DBP were higher in the patients than in the controls ($p = 0.021$ and $p = 0.009$; Table 2). One of the patients had a previous myocardial infarction (MI). The level of hsCRP was increased in the

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*Table 1*. Patient characteristics. Values are n (%) or median (IQR).

| Variables | Patients with JIA, n = 85 | Controls, n = 46 |
|---|---|---|
| Male | 20 (25) | 9 (20) |
| Age, yrs | 38.6 (35.0–40.6) | 37.7 (34.6–40.4) |
| Disease duration, yrs | 29.2 (28.2–30.6) | — |
| Onset age, yrs | 8.9 (5.2–11.6) | — |
| JIA category distribution | | |
| Systemic arthritis | 4 (5) | |
| RF-negative polyarthritis | 12 (14) | |
| RF-positive polyarthritis | 5 (6) | |
| Persistent oligoarthritis | 15 (18) | |
| Extended oligoarthritis | 14 (17) | |
| Enthesitis-related arthritis | 18 (21) | |
| Psoriatic arthritis | 15 (18) | |
| Undifferentiated arthritis | 2 (2) | |
| Current medication at 29-yr followup | | |
| Anti-TNF | 25 (29) | |
| Methotrexate | 19 (22) | |
| NSAID daily | 23 (27) | |
| Prednisolone | 5 (6) | |
| Health status in the patients with JIA at 29-yr followup | | |
| PGA, 10-cm VAS | 1.5 (0.5–2.4) | |
| No. active joints | 1 (0–2) | |
| No. joints LROM | 3 (1–7) | |
| PtGA, 10-cm VAS | 1.8 (0.7–2.8) | |

IQR: interquartile range; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; anti-TNF: anti-tumor necrosis factor; NSAID: nonsteroidal anti-inflammatory drugs; PGA: physician's global assessment; VAS: visual analog scale; LROM: limited range of motion; PtGA: patient's global assessment.

*Table 2*. CV risk factors in patients with JIA and controls. Values are mean (SD) or median (IQR) unless otherwise specified.

| Variable Assessed at 29-yr Followup | Patients with JIA, n = 85 | Controls, n = 46 | p |
|---|---|---|---|
| BMI, kg/m$^2$ | 25.7 (5.3) | 25.3 (4.2) | 0.629 |
| Waist circumference, cm | 92.6 (13.0) | 93.0 (10.2) | 0.849 |
| Daily smokers, n (%) | 20 (24) | 5 (11) | 0.077 |
| Pack-yrs of smoking | 0.01 (0.0–8.6) | 0.1 (0.0–2.9) | 0.469 |
| CVD in first-degree relative, n (%) | 48 (57) | 21 (46) | 0.260 |
| SBP, mmHg | 120 (15) | 114 (9) | 0.021 |
| DBP, mmHg | 76 (10) | 71 (8) | 0.009 |
| Hypertension, n (%) | 9 (11) | 0 (0) | 0.026 |
| Myocardial infarction, n (%) | 1 (1.2) | 0 (0) | |
| Total cholesterol, mmol/l | 4.8 (1.1) | 4.9 (0.8) | 0.732 |
| Triglycerides, mmol/l | 1.0 (0.7) | 1.0 (0.5) | 0.968 |
| Glucose, mmol/l | 5.2 (0.5) | 5.1 (0.5) | 0.621 |
| HbA1c, n (%) | 5.4 (0.3) | 5.4 (0.4) | 0.372 |
| hsCRP, mg/l | 1.8 (0.7–4.9) | 0.7 (0.01–1.9) | 0.001 |
| Pro-BNP, pmol/l | 3.7 (1.7–6.9) | 4.8 (3.0–7.0) | 0.107 |
| Vigorous physical activity, h/week | 2.0 (0.4–3.8) | 2.0 (0.0–3.3) | 0.602 |
| Moderate physical activity, h/week | 2.0 (1.0–4.0) | 1.0 (0.5–2.6) | 0.046 |

CV: cardiovascular; JIA: juvenile idiopathic arthritis; IQR: interquartile range; BMI: body mass index; CVD: cardiovascular disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycosylated hemoglobin; hsCRP: high-sensitivity C-reactive protein; Pro-BNP: prohormone of brain natriuretic peptide.

patients compared with the controls (p = 0.001). The patients with JIA reported participating in more physical activity of a moderate intensity than the controls (p = 0.046).

*LV morphology and function in patients and controls*. Of the 85 patients with JIA, 1 had a moderate aortic regurgitation, and 1 had a moderate tricuspid regurgitation. Of the 46 controls, 3 had a mild to moderate mitral regurgitation. No other abnormalities were found.

In general, the patients and controls were comparable concerning the variables of systolic function (Table 3). However, the interventricular septum diameter (IVSd) was thicker in the patients than in the controls (p = 0.036). The echocardiographic variables of diastolic function were within the normal range for the patients (Table 4). Seventy-five patients had normal E/e' values (< 8), 8 patients had

*Table 3*. LV dimensions and systolic function. Values are the mean (SD) unless otherwise specified.

| Variable Assessed at 29-yr Followup | Patients with JIA, n = 85 | Controls, n = 46 | p |
|---|---|---|---|
| Heartrate, bpm | 66.3 (10.9) | 63.1 (9.7) | 0.095 |
| LV IDd, cm | 5.1 (0.4) | 5.1 (0.4) | 0.459 |
| LV PWd, cm | 0.7 (0.1) | 0.7 (0.1) | 0.782 |
| IVSd, cm | 0.8 (0.2) | 0.7 (0.1) | 0.036 |
| LV EDV, ml | 90.8 (19.3) | 91.9 (20.0) | 0.774 |
| LV EF, % | 59.6 (3.6) | 60.2 (3.3) | 0.341 |
| LV FS, % | 33.6 (5.5) | 33.1 (5.1) | 0.599 |
| LV global strain, % | –18.2 (2.5) | –18.7 (2.0) | 0.281 |
| LV s' septal, cm/s | 8.2 (1.3) | 8.4 (1.4) | 0.668 |
| LV SV, ml | 67.9 (12.1) | 68.0 (12.2) | 0.970 |
| LV CI, l/min/m$^2$ | 2.4 (0.5) | 2.3 (0.3) | 0.144 |

LV: left ventricle; JIA: juvenile idiopathic arthritis; IDd: internal diameter in end-diastole; PWd: posterior wall diameter in end-diastole; IVSd: septum diameter in end-diastole; EDV: end-diastolic volume; EF: ejection fraction; FS: fractional shortening; s': mitral annular velocity in systole; SV: stroke volume; CI: cardiac index.

*Table 4*. LV diastolic function and LA dimensions. Values are mean (SD) or median (IQR) unless otherwise specified.

| Variables Assessed at 29-yr Followup | Patients, n = 85 | Controls, n = 46 | p |
|---|---|---|---|
| LV E, m/s | 0.7 (0.1) | 0.7 (0.1) | 0.272 |
| LV A, m/s | 0.5 (0.1) | 0.5 (0.1) | 0.616 |
| LV E/A ratio | 1.5 (0.4) | 1.4 (0.4) | 0.926 |
| LV DT, ms | 165 (36) | 180 (40) | 0.029 |
| LV IVRT, ms | 101 (14) | 99 (13) | 0.517 |
| LV e' septal, cm/s | 10.1 (2.2) | 10.1 (1.8) | 0.942 |
| LV e' lateral, cm/s | 13.5 (3.2) | 14.2 (2.7) | 0.208 |
| LV E/e' septal | 7.4 (1.6) | 7.2 (2.1) | 0.651 |
| LV E/e' lateral | 5.3 (4.6–6.3) | 4.8 (3.9–5.7) | 0.036 |
| LA area, cm$^2$ | 16.4 (2.9) | 15.1 (2.8) | 0.015 |
| LA area index, cm$^2$/m$^2$ | 8.9 (1.4) | 8.2 (1.3) | 0.005 |

LV: left ventricle; LA: left atrium; IQR: interquartile range; E: peak early transmitral flow velocity; A: peak late transmitral flow velocity; E/A ratio: peak early-to-late ratio mitral flow velocity; DT: E wave deceleration time; IVRT: isovolumic relaxation time; e': mitral annular velocity in diastole.

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borderline elevated values (8–12), and none of the patients had values above 12. However, compared with the controls, the mitral E wave DT was lower (p = 0.029), and the lateral E/e' and LA area were higher (p = 0.036 and p = 0.015) in the patients.

Intraobserver reproducibility for echocardiographic variables was good with CR for IVSd (0.2 cm), LV internal diameter in end-diastole (0.3 cm), FS (5.7%), e' septal (3 cm/s), E (0.2 m/s), E/A (0.9), E/e' (0.2), DT (61 ms), EF (7.2%), and end-diastolic volume (21.2 ml).

*The influence of the inflammatory burden and disease severity on LV diastolic function*. Lateral E/e' was higher in the patients with hsCRP ≥ 2 mg/l, a polyarticular disease course, and/or ≥ 3 joints with a limited range of motion (LROM) at the 29-year followup than in patients with less severe disease (p = 0.004, p = 0.050, and p = 0.016, respectively; Figure 1).

A longer duration of active disease was positively correlated with the E/A ratio and the lateral E/e' in the patients (p = 0.011 and p = 0.023; Table 5). Additionally, higher ESR AUC, higher CRP AUC, and more years receiving daily prednisolone correlated with a higher lateral E/e' (p = 0.042, p = 0.033, and p = 0.021, respectively).

The predictors of lateral E/e' in the patients were identified by multiple linear regression analyses. The variables significantly associated with lateral E/e' in Spearman correlation analysis (Table 5), as well as age and sex, were analyzed. Age (p = 0.010) and the duration of active disease (p = 0.046) were identified as predictors of lateral E/e' (data not shown).

*ECG findings in patients and controls*. ECG were recorded from 73 patients and 46 controls. Two patients had pathologic ECG [i.e., Wolff-Parkinson-White syndrome (1 patient) and LV hypertrophy (1 patient)]. Four patients had borderline ECG (unspecific ST segment and T waves alterations). All the controls had normal ECG. There was no difference in the QTc interval between the patients and the controls (418 ± 20 ms vs 415 ± 17 ms, p = 0.409). The heartrate was higher in the patients than in the controls (68 ± 13 bpm vs 60 ± 8 bpm, p = 0.001).

## DISCUSSION

In the present followup study of patients with JIA with longterm active disease, we found that the patients had a slightly altered LV morphology and diastolic function, but similar systolic function compared with the matched controls. The diastolic function was more impaired in the patients with a higher disease burden (i.e., high hsCRP, a polyarticular disease course, and/or numerous joints with LROM). Additionally, disease variables reflecting the cumulative inflammatory burden such as a long duration of active disease, CRP AUC and ESR AUC, and longterm prednisolone use were significantly correlated with a higher

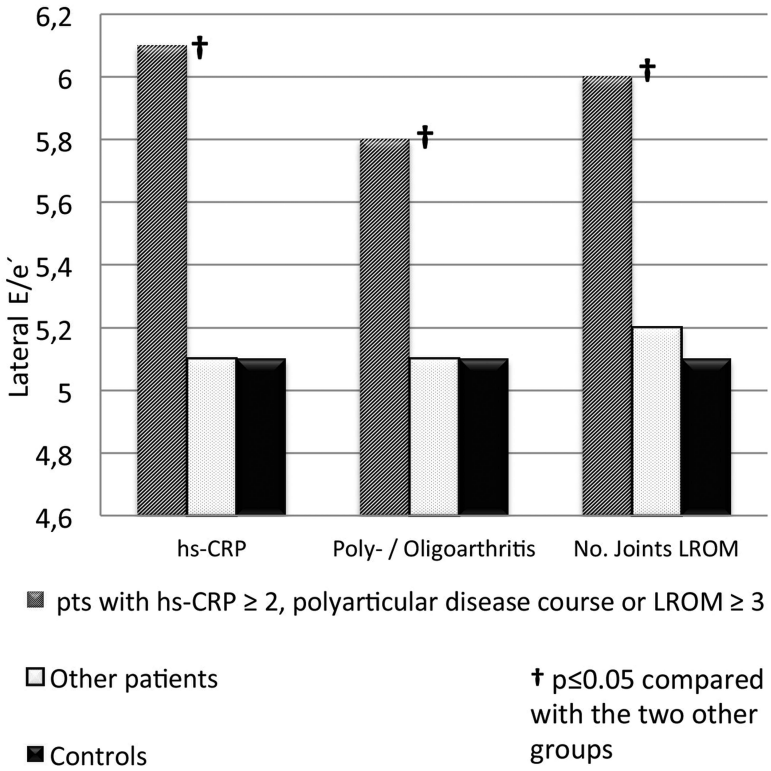


*Figure 1*. LV E/e' according to disease status assessed at 29-year followup. LV: left ventricular; E/e': filling pressure; hs-CRP: high-sensitivity C-reactive protein; LROM: limited range of motion.

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*Table 5*. The relation between cumulative inflammatory burdens and LV diastolic function at 29-year followup in patients with JIA. Values are $r_{sp}$ (Spearman correlation coefficient) unless otherwise specified.

| Variable | Median (IQR) | LV E/A Ratio | LV DT, ms | LV e' Septal, m/s | LV e' Lateral, m/s | LV E/e' Septal | LV E/e' Lateral | LA Area, cm |
|---|---|---|---|---|---|---|---|---|
| Duration of active disease* | 12.1 (7.0–14.4) | 0.277† | 0.019 | 0.018 | –0.125 | 0.141 | 0.249† | –0.009 |
| ESR AUC | 33.5 (22.5–51.0) | –0.004 | –0.117 | –0.052 | –0.109 | 0.179 | 0.229† | 0.085 |
| CRP AUC | 8.5 (5.0–18.8) | 0.070 | –0.038 | 0.081 | –0.014 | 0.133 | 0.236† | 0.200 |
| Yrs receiving prednisolone | 0.04 (0.0–1.1) | 0.123 | –0.171 | 0.049 | –0.126 | 0.108 | 0.253† | –0.038 |

* Assessed at 15-year followup. † $p < 0.05$. LV: left ventricle; JIA: juvenile idiopathic arthritis; IQR: interquartile range; E/A ratio: peak early-to-late ratio mitral flow velocity; E: peak early transmitral flow velocity; A: peak late transmitral flow velocity; DT: E wave deceleration time; e': mitral annular velocity in diastole; LA: left atrium; ESR: erythrocyte sedimentation rate; AUC: area under the curve; CRP: C-reactive protein.

lateral E/e'. To our knowledge, this is the first study evaluating cardiac function in adults with longterm JIA.

The finding of a comparable LV systolic function in patients and controls contrasts with reports from Bharti, *et al*, and Oguz, *et al,* who found an impairment of LV systolic function, reflected by a decreased EF, in children and adolescents with JIA[26,27]. Further, Bharti, *et al* and Alkady, *et al* have reported a larger end-diastolic diameter in children with JIA compared with controls[26,28]. All the values were within normal limits in these studies[26,27,28].

The interventricular septum was slightly thicker in the patients than in the controls in our study, which might be associated with the mildly higher blood pressure in the patient group[29].

Diastolic function is mainly dependent on myocardial relaxation and LV load[30]. The similar transmitral E and A velocities, and IVRT in the patients and controls, indicate that LV relaxation was not affected in the patients with JIA[21]. However, the lower mitral DT combined with the higher (lateral) E/e' ratio and the larger LA area indicate that the patients with JIA had higher LV-filling pressures than the controls[22,31,32]. An increased LV-filling pressure is usually associated with diastolic dysfunction and heart failure[33,34]. Although the diastolic variables in the patients with JIA were all within normal limits, the deviation from the control values indicates a marginal but definite impairment of diastolic LV function.

Previous studies in children and adolescents with JIA have reported an impairment of diastolic function expressed by a decreased transmitral E/A ratio and a longer IVRT that usually indicates an alteration in LV relaxation properties[26,28,35,36]. Our study confirms the finding of an increased E/e' in children with JIA compared with controls from Koca, *et al*[36]. However, most of the previous studies were conducted in children (mean age 9–15 yrs), and in the studies by Bharti, *et al* and Alkady, *et al*, more than 20% of the patients were in the systemic JIA category. This compared with our data with a frequency of 5%, which is representative of the prevalence of systemic JIA in Scandinavia.

The data on the pathogenesis linking inflammation and diastolic dysfunction are limited. It has been proposed that systemic inflammation may induce oxidative stress in the coronary microvascular endothelium, causing stiffening and hypertrophy of the cardiomyocytes that leads to increased LV diastolic stiffness[37]. Small vessel ischemic disease could also have contributed to the findings of a higher LV-filling pressure in our study. However, the definite mechanism for diastolic dysfunction in JIA remains elusive and calls for further study.

The ECG evaluation showed that the QTc interval was equal in both the patients and the controls. The higher heartrate found in the patients leaves less time for myocardial relaxation and may be explained by inflammation. Our study confirms the findings of Koca, *et al*, who did not find any difference in the QTc interval in 50 children and adolescents with JIA compared with controls[35].

Interestingly, we observed that the diastolic function was more impaired in the patients who had experienced a larger burden of inflammation, more severe disease, and prolonged daily prednisolone use compared with the patients with less severe disease. This suggests a relationship between immune dysregulation and subclinical diastolic dysfunction in JIA, and one might speculate whether today's aggressive treatment approach for the suppression of systemic inflammation in JIA is also instrumental for the prevention of CVD in these patients.

Our results correspond to the previously reported associations among JIA disease and treatment variables, markers of arterial stiffness, and DBP found in the same patient cohort[11]. Prior studies have evaluated the association between inflammation and cardiac function. Liang, *et al* found a correlation between interleukin 6 and diastolic dysfunction in patients with RA in a large echocardiographic study[38], and an elevated CRP has been shown to be an independent predictor for the deterioration of myocardial function in asymptomatic adult individuals without CVD[39]. The association between corticosteroids and CVD is difficult to measure because treatment with corticosteroids increases the risk of HTN and MI in patients with RA[40,41,42], but functions cardioprotectively by reducing inflammation.

*Strengths and limitations of our study*. The strengths of our study are the longterm followup of a well-defined cohort of

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patients with JIA and the presentation of novel data on cardiac function obtained by the blinded evaluation of comprehensive echocardiographic recordings. However, there are several limitations. Because multiple comparisons were performed, there is an inherent risk for Type I statistical error. Nevertheless, the consistent difference from the controls in the echocardiographic variables of diastolic dysfunction in the patients supports the validity of the findings. The number of patients included in our study was relatively small. However, out study remains the largest on cardiac function in patients with JIA. Because a cross-sectional study design was used for this cohort, the statistical relationships that were found indicate associations between variables and not necessarily any causal relationships.

The reproducibility for echocardiographic data is representative for the laboratory responsible for all echocardiographic data in the present study. Although recording and analysis of echocardiograms were obtained by 1 observer (HAA), this observer complied with the laboratory standards and was supervised in this context. Thus, we consider the reproducibility data given to be valid for our present study.

Adult patients with JIA with longterm active disease have comparable systolic function, but differ from controls in that they have a thicker interventricular septum and their diastolic variables indicate a higher LV-filling pressure. However, because the variables for cardiac morphology and diastolic function in patients with JIA are all within the normal range, the alterations are subclinical and do not infer specific treatment. There was an indication of higher LV-filling pressures in the patients with JIA with a large inflammatory burden, severe disease, and prolonged daily prednisolone use compared with the patients with less severe disease. These results point to a relationship between immune dysregulation and subclinical diastolic dysfunction in JIA and suggest the necessity of increased awareness for CV symptoms in patients with severe JIA.

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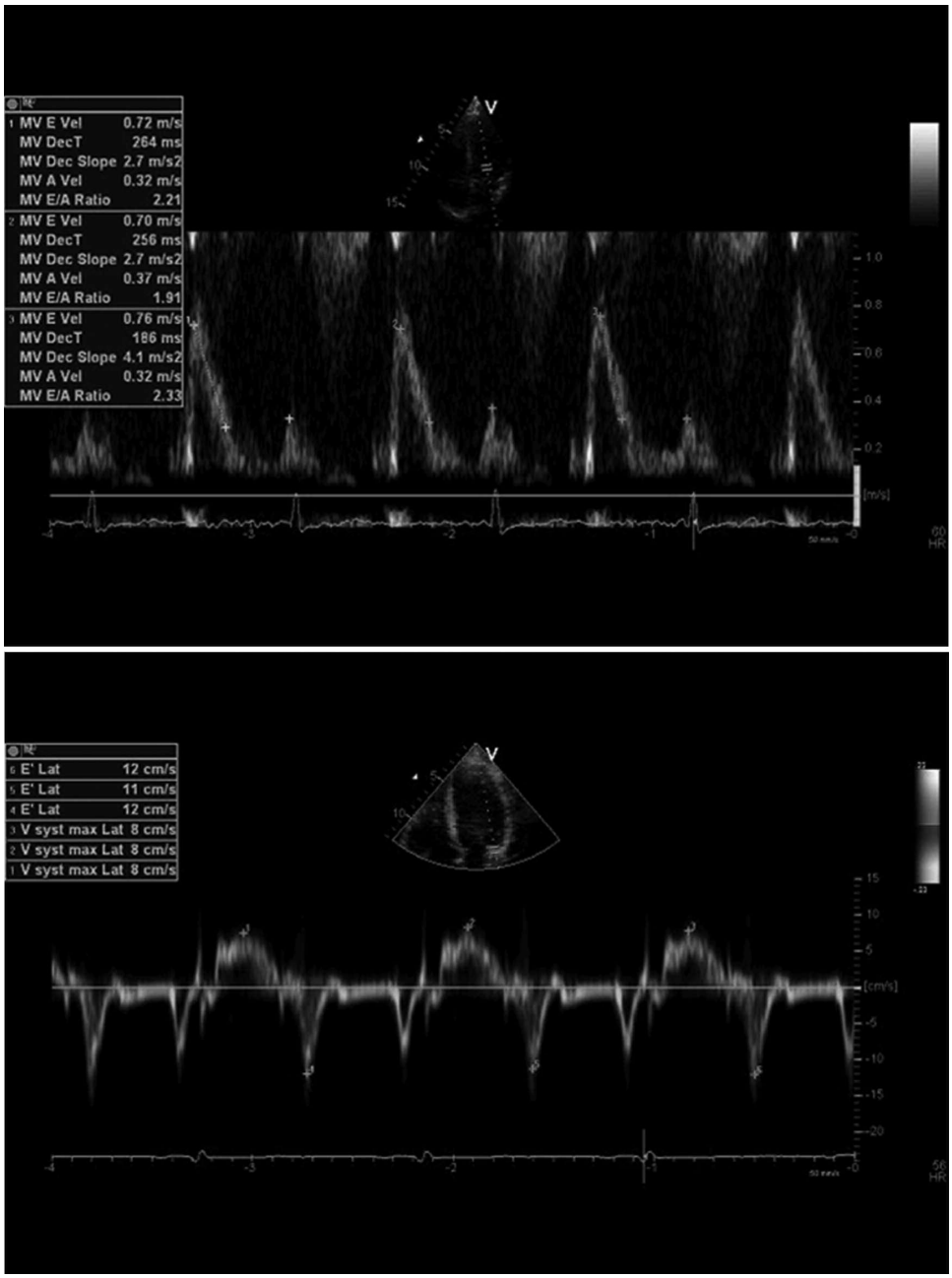
**APPENDIX 1.** Diastolic function as measured by echocardiography. Upper panel: LV transmitral recordings of early (E) and late (A) diastolic flow velocities from which the transmitral E/A ratio was calculated. Transmitral recordings of E wave deceleration time. Lower panel: LV mitral annular velocities in systole (LV s') and early diastole (LV e') measured in the septal and lateral mitral annulus with color tissue Doppler imaging. LV: left ventricular; E: peak early transmitral flow velocity; A: peak late transmitral flow velocity; E/A ratio: peak early-to-late ratio mitral flow velocity; s': mitral annular velocity in systole; e': mitral annular velocity in diastole.

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