EXTENDED REPORT

Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis

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Handling editor Tore K Kvien

ABSTRACT

Objective To compare arterial haemodynamics in adults with long-term juvenile idiopathic arthritis (JIA) to that of healthy controls, and explore the influence of traditional cardiovascular risk factors and JIA disease characteristics on arterial haemodynamics plus coronary artery calcification.

Methods 87 JIA patients (median age 38.4 years) with persistently active disease at least 15 years after disease onset (registered by longitudinal follow-up), were re-examined after median 29 years and compared with 87 matched controls. Arterial haemodynamics were characterised by arterial stiffness and blood pressure. Sphygmocor was used to measure the arterial stiffness markers pulse wave velocity (PWV) and augmentation index (Aix). Coronary calcification was assessed by CT.

Results Compared to controls, patients had significantly higher PWV (7.2 vs 6.9 m/s, p=0.035), and systolic and diastolic blood pressure (SBP, p=0.050 and DBP, p=0.029). Aix was numerically higher in the patients compared to the controls, but no statistically significant difference was found. Coronary calcification was present in 22 (26%) of the patients. Daily smoking was more frequent (p=0.043), and insulin resistance was higher (p=0.034) in patients than controls.

In patients, DBP, but no disease variables were determinants of PWV. Disease variables as well as traditional cardiovascular risk factors were associated with higher Aix, DBP and the presence of coronary calcification.

Conclusions JIA patients with long-term active disease had altered arterial haemodynamics compared with controls in our study. PWV was mainly determined by increased DBP, a parameter that again was associated with JIA disease and treatment variables.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease in childhood with an annual incidence of approximately 15 per 100 000 children.1 About 50% of those affected have active disease when they reach adulthood.3,4 Adult-onset chronic inflammatory arthritides have been strongly associated with an increased risk of cardiovascular disease (CVD),6 but cardiovascular risk in long-standing JIA has not been explored.

Non-invasive methods may detect vascular dysfunction as surrogate markers of subclinical CVD. Arterial pulse wave velocity (PWV) is a marker of large arterial stiffness and augmentation index (Aix) reflects arterial stiffness by a combination of pulse wave reflection, left ventricular ejection and heart rate.7 Coronary artery calcification is a marker of coronary atherosclerosis and may be quantified by CT.8 These markers are associated with subsequent CVD and all-cause mortality in diverse populations.4,9–14 Increased blood pressure (BP) is a well-known risk factor of cardiovascular morbidity and mortality.15

Data on arterial properties in JIA are scarce. Vlahos et al16 found impaired endothelial function in 30 children with JIA compared to controls, and Breda et al17 recently found an increased carotid intima media thickness in 38 JIA children compared to controls.16,17 Previous studies on BP in JIA have showed contradictory findings.16–19

The aim of the present study was to identify if JIA patients have increased arterial stiffness and BP by comparing arterial haemodynamics in a cohort of well-characterised adult JIA patients with long-term active disease to that of age-matched and gender-matched controls, and to assess coronary artery calcification in the JIA patients. We also wanted to determine a possible influence of traditional cardiovascular risk factors and JIA disease characteristics on the level of arterial haemodynamics and coronary artery calcification.

PATIENTS AND METHODS

Patients and controls

The 87 JIA patients included were selected from a large JIA cohort described in detail elsewhere.5,20,21 This cohort included 254 JIA patients who were, for the first time, referred to Oslo University Hospital (OUH) from 1980 to 1985, and later examined clinically after median 15 years of disease duration (15-year follow-up), and by mailed questionnaires after median 23 years (23-year follow-up).5,20,21 Medical records had been reviewed for information about variables related to disease onset and early disease course.

After median 29 years of disease duration, the patients who did not have active disease at the 15-year and/or 23-year follow-up, received a mailed questionnaire for the interception of possible patients with relapses. The 134 patients in the original cohort still having active disease at the 15-year, 23-year and/or 29-year follow-up, were invited to participate. Ninety (67%) of the 134 eligible JIA patients consented and were enrolled in...
an extended clinical examination at OUH, between May 2011 and March 2012 (29-year follow-up). Thirty-six patients did not respond to the invitation and eight chose not to participate. Three patients were excluded from the study after enrolment because of pregnancy. Retrospective analyses of data from the 134 eligible patients at the 15-year follow-up did not show any differences regarding gender, disease duration, or measures of disease activity and severity between the 87 patients included and the 47 eligible but not participating patients (data not shown). However, the non-participants were median 5.1 years younger than the participants.

Age-matched and gender-matched controls (n=87) were randomly selected from the Norwegian population register. Responders with a history of diabetes mellitus or inflammatory arthritis were not included.

The study was approved by the Regional Ethics Committee for Medical Research, and all participants provided written informed consent according to the declaration of Helsinki (2008).

**Clinical examination and cardiovascular risk assessment**

Clinical examination of the 87 patients was carried out by a specialist in rheumatology (BF, AMS or VL) and included the 71-joint count, general organ status, and physician’s global assessment of disease activity (10 cm VAS). The patients were classified according to the International League of Associations for Rheumatology classification criteria.22 Active disease was defined as the absence of remission off antirheumatic medication, and included patients with clinically active disease or inactive disease on antirheumatic medication.23 Clinical examination of the controls was done by the first author (HAA).

Body Mass Index (BMI) and waist circumference were measured in all participants.

Patients and controls were interviewed about comorbidity and family history of premature CVD, defined as a first-degree relative having CVD before the age of 55 in men and 65 in women. Systolic BP (SBP) and diastolic BP (DBP) were obtained in patients and controls after 5 min rest in a supine position, and Systolic BP (SBP) and diastolic BP (DBP) were obtained in all participants.

**Assessment of arterial stiffness and coronary artery calcification**

Sphygmocor apparatus (Atcor Medical, Sydney, Australia) was used to measure PWV and AIx in patients and controls. All assessments were done by the first author (HAA). The participants did not eat, drink (except water) or smoke for at least 3 h before the examination.

To measure PWV, pulse wave forms from the right common carotid artery and the left femoral artery were obtained transcutaneously and gated to an electrocardiogram for the assessment of transit time. The PWV was calculated from the surface distance between the two recording sites divided by the time delay between the feet of the two waveforms.9 Measurements met the automatic quality control (specified by Sphygmocor apparatus) and the mean from two measurements with a difference of <0.5 m/s was used for calculation.

AIx was defined as the difference between the second and first systolic peaks of the central pressure waveform, expressed as a percentage of the pulse pressure and standardised to a heart rate of 75 bpm.9 The aortic pressure waveform was estimated from recordings of the radial artery waveform by use of a transfer system.25 The average of three measurements, all having a quality index score >85%, was used for statistical analysis. Measurements of sufficient quality were obtained in 78 patients and 84 controls for PWV, and in 79 patients and 87 controls concerning AIx.

To detect and quantify coronary artery calcification score, 84 patients were scanned on a 320-detector row CT scanner (Aquilion ONE, Toshiba Medical Systems). One radiologist (AG) used a dedicated workstation (Vitrea IX, Vital Images, Minnetonka) with a computerised program (Coronary Artery Calcium Scoring) with a threshold of 130 Hounsfield units (HU) to calculate the amount of coronary calcification as an Agatston score.10 22 Only patients underwent coronary calcification scoring.

**Questionnaires**

Patients and controls completed a self-reported questionnaire about smoking habits and physical activity. The short International Physical Activity Questionnaire was used to assess total work and leisure time physical activity.26 27

**Laboratory assessments**

Blood was drawn after an overnight fast in patients and controls and analysed for low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol, triglycerides, high sensitivity C-reactive protein (hs-CRP), glucose, glycated haemoglobin (HbA1c), and insulin. The homeostasis model assessment for insulin resistance (HOMA-IR) was derived from the assessments of insulin and glucose.28 One JIA patient had diabetes type 2 and was not included in analyses concerning glucose, HbA1c and insulin. Area under the curve (AUC) was calculated either from parameters measured at disease onset, 15-year and the current visits (erythrocyte sedimentation rate (ESR) and platelets), or at the 15-year and the current visits (CRP).

**Statistics**

Comparisons between JIA patients and matched controls were done by two-tailed paired sample t test for continuous normally distributed variables, Wilcoxon’s rank sum test for continuous not normally distributed values, and McNemar’s test for categorical variables.

Age-adjusted and gender-adjusted linear regression analyses were used to investigate associations between traditional cardiovascular risk factors as well as disease variables and arterial haemodynamics. To identify determinants of PWV and AIx, candidate factors associated with PWV and AIx in the initial analyses (p<0.12), and age and gender, were tested in the subsequent multivariate analyses with backward deletion of possible determinants. Highly intercorrelated (r>0.7) independent variables were avoided in the multivariate analyses. Missing values in the multiple regression analyses were replaced with mean or median values. No variable had more than 5% missing parameters.

Age-adjusted and gender-adjusted logistic regression analyses were used to investigate associations between traditional cardiovascular risk factors and disease variables, and coronary artery calcification. Agatston score dichotomised to Agatston>0 or Agatston=0 was used as the dependent variable. The strength of the associations was given as ORs with 95% CI.

SPSS V20 (SPSS, Chicago, USA) was used for the statistical analyses.

**RESULTS**

**Demographics and traditional cardiovascular risk factors**

Table 1 summarises the patient characteristics.

A higher percentage of the JIA patients than the controls were daily smokers (25% vs 13%, p=0.043, table 2). Arterial
hypothesis was present in 11% of the patients and 2% of the controls (p=0.039). The levels of HOMA-IR and hs-CRP were higher in the patients than the controls (p=0.034 and p=0.001, respectively). The JIA patients reported that they performed more physical activity of moderate intensity than the controls (p=0.001).

Arterial haemodynamics and coronary artery calcification at 29-year follow-up

PWV was, on average, 7.2 m/s in the patients and 6.9 m/s in the controls (p=0.035, table 3). Alx also tended to be higher in the patients than the controls, but no statistically significant difference was found (p=0.154). The SBP and DBP were higher in patients than controls (p=0.050 and p=0.029, respectively). 22 of 84 JIA patients (26%) had a coronary calcification score above zero, including six patients (7%) with a score above 10, and 16 patients (19%) with a score from 1 to 10. The difference in PWV between the patients and controls was no longer statistically significant when adjusted for DBP.

Associations between traditional cardiovascular risk factors and arterial stiffness in JIA patients at 29-year follow-up

In age-adjusted and gender-adjusted linear regression analyses, higher SBP and DBP were associated with increased PWV (p<0.001, table 4) in the JIA patients. Higher pulse rate (p=0.003), lower levels of HDL cholesterol (p=0.050) and elevated blood glucose (p=0.001) were also associated with increased PWV. Higher SBP (p=0.001) and DBP (p<0.001) and less vigorous physical activity (p=0.004) were associated with higher Alx.

Associations between disease variables assessed at 29-year follow-up and arterial haemodynamics

In linear regression analyses adjusted for age and gender, higher hs-CRP at 29-year follow-up (ß=0.662, p=0.004) was associated with higher Alx in the patients. Patients’ global assessment of wellbeing was associated with increased DBP (ß=0.125, p=0.043). Current physician’s global assessment of disease activity, numbers of active and mobility-restricted joints, and use of antitumor necrosis factor (anti-TNF) did not correlate with PWV, Alx or DBP (data not shown).

Longitudinal and cumulative disease variables related to arterial haemodynamics

In the JIA patients, none of the disease variables assessed cumulatively or at 15-year follow-up showed any statistically significant association with PWV (table 5). Higher physician’s global

Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>JIA patients (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Male gender; n (%)</td>
<td>20 (23)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>38.4 (34.8–40.6)</td>
</tr>
<tr>
<td>Disease duration (years)*</td>
<td>29.2 (28.2–30.6)</td>
</tr>
<tr>
<td>Onset age (years)*</td>
<td>8.8 (4.7–11.7)</td>
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<tr>
<td>JIA subtype distribution</td>
<td></td>
</tr>
<tr>
<td>Systemic arthritis; n (%)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>RF negative polyarthritis; n (%)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>RF positive polyarthritis; n (%)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Persistent oligarthritis; n (%)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Extended oligarthritis; n (%)</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Enthesitis-related arthritis; n (%)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Psoriatic arthritis; n (%)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Unclassified; n (%)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Current medication at 29-year follow-up</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF; n (%)</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Methotrexate; n (%)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>NSAIDs daily; n (%)</td>
<td>23 (26)</td>
</tr>
<tr>
<td>Prednisolone; n (%)</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

*Median (IQR).

Table 2  Traditional cardiovascular risk factors in JIA patients and controls

<table>
<thead>
<tr>
<th>Variable assessed at 29-year follow-up</th>
<th>JIA patients (n=87)</th>
<th>Controls (n=87)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²); mean (SD)</td>
<td>25.7 (5.3)</td>
<td>25.9 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference (cm); mean (SD)</td>
<td>92.6 (13.0)</td>
<td>94.2 (11.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers; n (%)</td>
<td>30 (35)</td>
<td>26 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily smokers; n (%)</td>
<td>22 (25)</td>
<td>11 (13)</td>
<td>0.043</td>
</tr>
<tr>
<td>Ever smokers; n (%)</td>
<td>47 (55)</td>
<td>53 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-years of smoking (years)*</td>
<td>0.1 (0.0–9.0)</td>
<td>0.1 (0.0–6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>CVD in first degree relative; n (%)</td>
<td>50 (58)</td>
<td>41 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension; n (%)</td>
<td>10 (11)</td>
<td>2 (2)</td>
<td>0.039</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L); mean (SD)</td>
<td>4.8 (1.1)</td>
<td>5.0 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L); mean (SD)</td>
<td>3.0 (1.0)</td>
<td>3.0 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L); mean (SD)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L); mean (SD)</td>
<td>1.0 (0.7)</td>
<td>1.0 (0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mmol/L); mean (SD)</td>
<td>5.2 (0.5)</td>
<td>5.1 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c; mean (SD)</td>
<td>5.4 (0.3)</td>
<td>5.4 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>0.9 (0.4–1.4)</td>
<td>0.6 (0.4–1.1)</td>
<td>0.034</td>
</tr>
<tr>
<td>hs-CRP (mg/L)*</td>
<td>1.8 (0.8–5.2)</td>
<td>0.9 (0.01–2.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vigorous physical activity (hours/week)*</td>
<td>2.0 (0.5–4)</td>
<td>1.9 (0.0–3.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate physical activity (hours/week)*</td>
<td>2.0 (1.0–4.0)</td>
<td>1.0 (0.1–2.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Median (IQR).

BMI, Body Mass Index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HOMA-IR, the homeostasis model assessment for insulin resistance; hs-CRP, high sensitivity C-reactive protein; JIA, juvenile idiopathic arthritis; LDL, low density lipoprotein; NS, not statistically significant.

Table 3  Arterial haemodynamics and coronary artery calcification scores

<table>
<thead>
<tr>
<th>Variables assessed at 29-year follow-up</th>
<th>N</th>
<th>JIA patients</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (m/s); mean (SD)</td>
<td>78</td>
<td>7.2 (1.0)</td>
<td>6.9 (0.8)</td>
<td>0.035</td>
</tr>
<tr>
<td>Alx; mean (SD)</td>
<td>79</td>
<td>14.5 (10.8)</td>
<td>12.0 (12.2)</td>
<td>0.154</td>
</tr>
<tr>
<td>Pulse (bpm); mean (SD)</td>
<td>87</td>
<td>62.7 (10.7)</td>
<td>61.8 (9.7)</td>
<td>0.564</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg); mean (SD)</td>
<td>87</td>
<td>119.4 (14.5)</td>
<td>115.7 (9.8)</td>
<td>0.050</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg); mean (SD)</td>
<td>87</td>
<td>75.7 (10.3)</td>
<td>72.7 (8.2)</td>
<td>0.029</td>
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<tr>
<td>Coronary artery calcification, Agatston score 1–10; n (%)</td>
<td>84</td>
<td>16 (19)</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Coronary artery calcification, Agatston score &gt;10; n (%)</td>
<td>84</td>
<td>6 (7)</td>
<td>Not assessed</td>
<td></td>
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</tbody>
</table>

*Alx was normalised to a heart rate of 75 bpm.

Alix, augmentation index; JIA, juvenile idiopathic arthritis; PWV, pulse wave velocity.
The relation between cumulative or longitudinal JIA disease variables and arterial haemodynamics

### Table 5

<table>
<thead>
<tr>
<th>Variables assessed during 29-year follow-up</th>
<th>Linear regression analyses*</th>
<th>PWV</th>
<th>p Value</th>
<th>Alx</th>
<th>p Value</th>
<th>DBP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (unadjusted)</td>
<td></td>
<td>0.044</td>
<td>0.144</td>
<td>0.455</td>
<td>0.133</td>
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<tr>
<td>Male gender (unadjusted)</td>
<td></td>
<td>0.677</td>
<td>0.013</td>
<td>−0.022</td>
<td>0.014</td>
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<tr>
<td>Waist circumference</td>
<td></td>
<td>0.017</td>
<td>0.077</td>
<td>−0.037</td>
<td>0.704</td>
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<tr>
<td>BMI</td>
<td></td>
<td>0.042</td>
<td>0.091</td>
<td>−0.059</td>
<td>0.808</td>
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<tr>
<td>Systolic blood pressure</td>
<td></td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>0.259</td>
<td>0.001</td>
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<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td>0.056</td>
<td>&lt;0.001</td>
<td>0.398</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Pulse</td>
<td></td>
<td>0.033</td>
<td>0.003</td>
<td>0.154</td>
<td>0.178</td>
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<tr>
<td>CVD in first degree relative</td>
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<td>0.381</td>
<td>0.077</td>
<td>−0.378</td>
<td>0.878</td>
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<td>HDL cholesterol</td>
<td></td>
<td>−0.609</td>
<td>0.050</td>
<td>−0.447</td>
<td>0.888</td>
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<tr>
<td>Triglycerides</td>
<td></td>
<td>0.263</td>
<td>0.288</td>
<td>2.815</td>
<td>0.123</td>
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<tr>
<td>LDL cholesterol</td>
<td></td>
<td>0.105</td>
<td>0.368</td>
<td>−0.573</td>
<td>0.629</td>
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<tr>
<td>Glucose</td>
<td></td>
<td>0.715</td>
<td>0.001</td>
<td>3.262</td>
<td>0.153</td>
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<tr>
<td>HbA1c</td>
<td></td>
<td>0.650</td>
<td>0.073</td>
<td>2.411</td>
<td>0.506</td>
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<td>HOMA-IR</td>
<td></td>
<td>0.136</td>
<td>0.373</td>
<td>1.125</td>
<td>0.436</td>
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<tr>
<td>Package years</td>
<td></td>
<td>−0.004</td>
<td>0.837</td>
<td>0.139</td>
<td>0.456</td>
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<tr>
<td>Daily smoking</td>
<td></td>
<td>−0.081</td>
<td>0.792</td>
<td>4.352</td>
<td>0.113</td>
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<tr>
<td>Vigorous physical activity</td>
<td></td>
<td>−0.086</td>
<td>0.090</td>
<td>−1.455</td>
<td>0.004</td>
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<tr>
<td>Moderate physical activity</td>
<td></td>
<td>−0.018</td>
<td>0.439</td>
<td>−0.284</td>
<td>0.232</td>
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</table>

* Results of linear regression analyses adjusted for age and gender, with PWV, Aix and DBP as dependent variables.

**DISCUSSION**

In the present study, JIA patients with long-term active disease had slightly increased arterial stiffness assessed by PWV compared with matched controls. DBP and SBP were also increased in the JIA patients, while Aix was numerically, but not statistically, significantly higher. Coronary artery calcifications were significantly associated with Aix at age- and gender-adjusted analyses. Higher Aix was associated with higher levels of coronary artery calcification (score >0) in the JIA patients.

**Factors associated with coronary artery calcification**

Logistic age-adjusted and gender-adjusted regression analyses demonstrated that increased levels of waist circumference (OR=1.05; 95% CI 1.00 to 1.10), BMI (OR=1.13; 95% CI 1.01 to 1.26), SBP (OR=1.05; 95% CI 1.01 to 1.10), glucose (OR=3.26; 95% CI 1.08 to 9.79), and years on daily prednisolone (OR=1.14; 95% CI 1.02 to 1.27), were related to coronary calcification (score >0) in the JIA patients.
found in 26% of the patients. PWV was mainly determined by increased DBP, a parameter that again was associated with JIA disease and treatment variables. AIx was determined by traditional cardiovascular risk factors, physical activity, inflammatory variables, disease severity, and received antirheumatic medication. To our knowledge, this is the first study presenting data on cardiovascular risk in adults with JIA.

PWV, but not AIx was increased in the JIA patients compared to the controls. AIx and PWV are both indexes of arterial stiffness but cannot be used interchangeably. While carotid-femoral PWV is a direct measure of large arterial stiffness, AIx is an indirect measure of arterial stiffness that quantifies the combination of the amplitude from the reflected peripheral wave, the forward pressure from left ventricular contraction and the heart rate. AIx is found to have predictive value for CVD in selected forward pressure from left ventricular contraction and the heart rate but cannot be used interchangeably. While carotid-femoral PWV is a direct measure of large arterial stiffness, AIx is an indirect measure of arterial stiffness that quantifies the combination of the amplitude from the reflected peripheral wave, the forward pressure from left ventricular contraction and the heart rate. AIx is found to have predictive value for CVD in selected diseases, but PWV is accepted as the ‘gold standard’ for the assessment of arterial stiffness because of its well-documented ability to predict CVD.

The mean PWV in the patients was 7.2 m/s, a value lower than what has been considered clinically significant (10 m/s) for the prediction of cardiovascular events. However, our patients were only median 38.4 years, 25 years younger than the general population this threshold represents. The difference in mean PWV between patients and controls was 0.3 m/s, and the clinical significance of such a small difference is unclear. Recent data from a meta-analysis showed that a 1 m/s increase of PWV corresponded to a 15% increased risk of cardiovascular and all-cause mortality suggesting that a 0.3 m/s increase of PWV may be associated with increased cardiovascular risk.

Data on arterial stiffness in JIA have been limited to two studies. Vlahos et al. found no difference in PWV in 30 children and adolescents with JIA compared to controls. By contrast, Argyropoulou et al. found increased PWV as measured by MRI in 31 children and young adults with JIA. However, the method used by Argyropoulou et al. was different from the one used in our study, and both studies were mainly done in children.

Some traditional cardiovascular risk factors, such as daily smoking, arterial hypertension and insulin resistance were increased in the JIA patients compared to the controls. We cannot exclude that these traditional risk factors have influenced the increased PWV measured in the patients. On the other hand, most traditional cardiovascular risk factors, such as BMI, waist circumference, pack-years of smoking, CVD in the family, and serum cholesterol profiles were comparable between the patients and the controls.

Our finding of increased daily smoking is in contrast with an earlier case-control on adolescents with JIA. Studies on serum cholesterol levels in JIA have shown conflicting results, but these studies have mainly been done in children. Hypertension and BP have been associated with increased arterial stiffness in the general population. On the other hand, aortic stiffness has been identified as a predictor of future hypertension in normotensive individuals indicating a bidirectional relationship of arterial stiffness and hypertension.

This study is the first on coronary artery calcification in JIA. While 26% of the patients had detectable coronary calcification, 7% had coronary calcification scores above 10. This frequency is not different from what has been found in a large study including asymptomatic individuals of comparable age.

Several parameters of cumulative inflammatory burden (duration of active disease, CRP AUC and platelets AUC) were associated with AIx, but not with PWV. ESR AUC was associated with increased DBP. Similar results were found in a recent follow-up study of rheumatoid arthritis (RA) patients. CRP has also been demonstrated to be a strong predictor of CVD in healthy individuals. Our finding is in accordance with the study by Argyropoulou who did not find any association between CRP nor use of antirheumatic medication and PWV.

We found that treatment with prednisolone was a predictor of AIx and a correlate to DBP and coronary calcification. The net effects of antirheumatic medication on CVD risk is not easy to evaluate since the possible cardioprotective effect of reducing

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**Table 6** Determinants of arterial stiffness in adults with JIA

<table>
<thead>
<tr>
<th>Multiple linear regression analysis*</th>
<th>PWV (n=78)</th>
<th>AIx (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constant</strong></td>
<td>β 1.561</td>
<td>β -32.658</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>SE 1.142</td>
<td>SE 10.035</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>p 0.176</td>
<td>p 0.002</td>
</tr>
<tr>
<td><strong>Variables assessed at 29-year follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td>β 0.056</td>
<td>β 0.336</td>
</tr>
<tr>
<td><strong>Daily smoking</strong></td>
<td>SE 0.010</td>
<td>SE 0.089</td>
</tr>
<tr>
<td><strong>Vigorous physical activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative and longitudinally variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of joints with limited range of motion at 15-year follow-up</strong></td>
<td>0.032</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Years on daily prednisolone</strong></td>
<td>0.433</td>
<td>0.207</td>
</tr>
</tbody>
</table>

*Final model of multiple linear regression analyses with backward deletion of possible determinants of higher AIx and PWV. Variables associated with PWV and AIx in the age-adjusted and gender-adjusted linear regression analyses (p<0.12, see tables 4 and 5 and online supplementary table S1) as well as age and gender were analysed. R squared for PWV=0.364 and for AIx=0.577.

AIx: augmentation index; JIA: juvenile idiopathic arthritis; PWV: pulse wave velocity.
inflammation may be counterbalanced by drug side effects or the possible influence of disease severity as marked by extended medication. Our findings correspond to the literature where use of corticosteroids has been associated with increased risk of hypertension and myocardial infarction in RA patients.46–48

Analyses of self-reported measures of physical activity indicated that vigorous physical activity was associated with decreased AIx in our patients. Although these data should be interpreted with caution, they suggest that performing physical activity may have a preventive cardiovascular effect in JIA patients.

The strength of this study is the thorough collection of comprehensive data in a well-defined cohort of JIA patients presenting new knowledge of arterial haemodynamics and cardiovascular risk profile in adults with JIA. The limitation is the small number of participants and their young age that made the comparison of cardiovascular events and atherosclerosis difficult.

In this study, adults with JIA had slightly increased PWV, a marker of large artery stiffness, compared with controls, and 26% had coronary artery calcification. JIA patients had higher BP than controls, and DBP was the most consistent correlate of PWV. None of the disease variables correlated with PWV, but JIA disease and treatment variables were associated with AIx and DBP.

Acknowledgements Torhild Garen for her help with preparation of questionnaires, Cathrine Brunborg for statistical support, Lars Markid for valuable help obtaining laboratory assessments and Inge-Margrethe Gilboe for administrative support.

Contributors The corresponding author confirms that all the individuals listed as authors fulfil the uniform authorship credit requirements for manuscripts submitted to medical journals, that is, that they all contributed to the manuscript based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Funding The project received financial support from the Norwegian Foundation for Health and Rehabilitation.

Competing interest None.

Patient consent Obtained.

Ethics approval The Regional Ethics Committee for Medical Research (Helse Øst-Dst).

Provenance and peer review Not commissioned; externally peer reviewed.

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Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis

Hanne A Aulie, Anne M Selvaag, Anne Günther, Vibke Lilleby, Øyvind Molberg, Anders Hartmann, Hallvard Holdaas and Berit Flatø

Ann Rheum Dis 2015 74: 1515-1521 originally published online April 2, 2014
doi: 10.1136/annrheumdis-2013-204804

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