

Distensibility and pulse wave velocity of the thoracic aorta in patients with juvenile idiopathic arthritis: An MRI study

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ABSTRACT

Objective. An increased incidence of cardiovascular disease has been found in rheumatic disorders. Changes in the variables of aortic elasticity in patients with juvenile idiopathic arthritis (JIA) were evaluated and their relationship to inflammation, anti-rheumatic drugs and traditional cardiovascular risk factors were investigated in this study.

Methods. Phase contrast MR was performed in 31 patients with JIA and 28 age and sex matched controls to evaluate the aortic distensibility and pulse wave velocity (PWV). Disease activity variables, plasma lipid profile, homocysteine, thyroid hormones, glucose and insulin were assessed in the patients.

Results. Eighteen patients had oligoarticular, 6 polyarticular and 7 systemic disease. Distensibility was lower (mean: 10.25; SD: 4.18) and PWV was higher (mean: 3.68; SD: 1.59) in the patients compared to the controls (mean: 13.4; SD: 4.99), (mean: 1.38; SD: 0.54) respectively ($p < 0.01$). A positive correlation between PWV and age was observed in the patients ($r_s = 0.47$, $p < 0.01$) and controls ($r_s = 0.72$, $p < 0.01$), and a negative correlation between distensibility and age in the patients ($r_s = -0.59$, $p < 0.01$) and controls ($r_s = -0.63$, $p < 0.01$). No statistically significant correlations were found between distensibility and PWV and metabolic and disease activity parameters. When distensibility and PWV were adjusted for age no significant differences were found between the three subtypes of JIA.

Conclusion. JIA is associated with increased aortic stiffness that might suggest subclinical atherosclerosis. Early detection and follow-up by non-invasive methods may be useful in the prevention of future cardiovascular disease.

Introduction

The most frequent cause of death in rheumatoid arthritis (RA) is cardiovascular disease (1,2). Predisposing factors for atherosclerosis in RA patients are systematic chronic inflammation, the use of anti-rheumatic medications (corticosteroids and methotrexate) and

a sedentary lifestyle (1,3). Since the above-mentioned risk factors also exist in juvenile idiopathic arthritis (JIA), an increased prevalence of atherosclerosis might be suspected in JIA patients. Early detection of atherosclerosis is important to implement appropriate prophylactic measures and treatment.

The early lesions of atherosclerosis may be expected to alter the elastic properties of the arterial wall (4-7). Distensibility and pulse wave velocity (PWV), measured by ultrasound and phase contrast MR, have been previously used for the evaluation of the passive mechanical properties of arteries (4-11).

Previous studies have demonstrated that either an acute or a chronic decrease in the aortic distensibility can affect coronary blood flow, leading to compromised myocardial perfusion even in the absence of coronary artery stenosis (6, 12). Phase contrast MR provides more direct information on the size and pulsation of the ascending and descending aorta than any other non-invasive technique and its usefulness in the evaluation of the aortic elastic properties is well documented (9-11).

To our knowledge, there has been no study evaluating the mechanical properties of the aortic wall in patients with rheumatic disorders. The purpose of this study was to measure in patients with JIA the distensibility and PWV of the thoracic aorta and to evaluate the influence of traditional cardiovascular risk factors, inflammatory factors and antirheumatic drugs on the elastic properties of the aorta.

Material and methods

Thirty-one patients with JIA, diagnosed according to the International League Against Rheumatism (ILAR) criteria (13), and 28 age- and sex-matched controls were included in this study. The patients included in the study were subjects who presented for a routine follow-up at our outpatient Pediatric Rheumatology Center. Disease activity was evaluated based upon the following: Ritchie's articular index (14), swollen joint count, grip strength, pain, duration of early morning stiff-

ness, blood hemoglobin, and erythrocyte sedimentation rate measurements. The index of disease activity (IDA) was evaluated according to a previously described method (15). Accumulated disease activity was assessed according to recorded information, as previously described by Baecklund (16).

The study was performed under institutional review board approval. Informed consent was obtained from the older children (age 18 years) and from the parents of all children.

Magnetic resonance imaging (MRI) was performed with a 1.5 Tesla unit, using a body coil and ECG triggering. Consecutive transverse and oblique sagittal images of the thoracic aorta were obtained with a standard spin-echo pulse sequence. A gradient-echo pulse sequence with the following characteristics – a velocity-encoding gradient, a repetition time equal to the RR interval of the subject's ECG, 5.5 msec repetition time; matrix size 256 x 256; field of view 300mm; slice thickness 6 mm, and a flip angle of 20° – was performed perpendicular to the ascending aorta at the level of the bifurcation of the pulmonary artery. Maximal velocity encoding was set at 200 cm/sec. This sequence resulted in 16 phase-related pairs of modulus and velocity-encoded images of the ascending and descending aorta. The flow through the ascending and descending aortas was calculated using the velocity-encoded images. PWV was calculated, in meters per second, as the ratio of the distance between the ascending and descending aorta (measured on oblique sagittal images) and the time difference between the arrival of the pulse wave at these levels. The pulse wave was considered to have arrived at a certain level when the flow reached half of its maximum value. Before and after imaging the systolic and diastolic blood pressures were measured from the brachial artery by a sphygmomanometer with the subject lying supine. Distensibility in mm/Hg was calculated using the following formula: $(A_{\max} - A_{\min}) / [A_{\min} \times (P_{\max} - P_{\min})]$ where A_{\max} = systolic area (mm²), A_{\min} = diastolic area (mm²), P_{\max} = systolic blood pressure (mm Hg), and P_{\min} = diastolic blood pressure (mm Hg).

All laboratory determinations were obtained after the patients had fasted for 12 hrs overnight. They included the measurement of serum lipid parameters [total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, apolipoproteins A1 and B, and lipoprotein (a)], free thyroxine (FT4), thyroid stimulating hormone (TSH), total triiodothyronine (TT3), C-reactive protein (CRP), plasma homocysteine, glucose, insulin, urea, creatinine and uric acid. Plasma homocysteine levels were measured by high performance liquid chromatography (17). High sensitive CRP was determined by Immunoturbidimetric method (Cobas, Integra, F. Hoffmann-La Roche, Basel, Switzerland). The techniques used for the determination of other parameters were previously described (18).

The statistical analysis was performed with SPSS Base 7.5 for Windows. Using the Kolmogorov-Smirnov test the normality of the distribution of the parameters was assessed. The Mann-Whitney U test was used to analyse the differences in PWV and distensibility between patients and controls. The relationships between the measured variables and PWV and distensibility were studied using the Spearman correlation coefficient. A p value < 0.05 was considered to be statistically significant.

Results

The control group consisted of 14 males and 14 females aged from 3.2 – 26.5 years (mean age 13 years). None of the subjects included in the control group had inflammatory disease or any other condition that could have affected the aortic elastic properties. The group of patients consisted of 15 males and 16 females aged from 3.4 to 26.2 years (mean age 13.6 years). Eighteen patients had oligoarticular, 6 polyarticular and 7 systemic disease. The duration of the disease ranged from 2 to 21.5 years (mean: 9.1; SD: 5.4), the duration of disease activity ranged from 0.33 to 16 years (mean: 3.9; SD: 4.4) and the age at onset ranged from 0.9 to 12.5 years (mean: 5.9 years; SD: 4.0). Rheumatoid factor and HLA B27 were negative in all patients, whereas

fluorescent antinuclear antibodies (titer 1/40) were positive in 17 patients.

All patients were normotensive, their functional class according to Steinbrocker was I or II and there was no difference in the total amount of daily physical exercise between patients and controls. CRP was increased (> 8 mg/L) in 7 patients ranging from 12–100 mg/L. Laboratory determinations regarding plasma lipid profile, homocysteine, thyroid hormones, glucose and insulin were within normal range. Twelve patients received corticosteroids at low dose (4 mg/day methylprednisolone).

Distensibility was lower in the patients (10.25 ± 4.18) compared to controls (13.4 ± 4.99) ($p < 0.01$) and PWV was higher in patients (3.68 ± 1.59) compared to controls (1.38 ± 0.54) ($p < 0.01$). In the group of patients a positive correlation between PWV and age was observed ($r_s = 0.47$, $p < 0.01$). A positive correlation was also found in the control group ($r_s = 0.72$, $p < 0.01$). Furthermore, a negative correlation between distensibility and age was found in the patients ($r_s = -0.59$, $p < 0.01$) and controls ($r_s = -0.63$, $p < 0.01$). Data regarding the aortic elastic properties and age of the three clinical subtypes are given in Table I. No statistically significant correlations were found between distensibility and PWV and CRP ($r_s = 0.087$, $r_s = 0.09$ respectively), or between the index of disease activity ($r_s = -0.10$, $r_s = 0.15$) and accumulated disease activity ($r_s = -0.20$, $r_s = 0.10$) or the duration of active disease ($r_s = -0.2$, $r_s = -0.03$). Moreover, no significant correlations were observed between aortic elastic properties and lipid parameters, plasma homocysteine, insulin, urea, creatinine, uric acid, blood glucose, serum thyroid hormone levels, the disease type, the cumulative dose of corticosteroids, or methotrexate administration. When distensibility and PWV were adjusted for age no significant differences were found between the three subtypes of JIA.

Discussion

Atherosclerosis is an inflammatory disease and does not result simply from the accumulation of lipids (19, 20). The

earliest lesion of atherosclerosis is the fatty streak which is common in infants and young children and it is a pure inflammatory lesion consisting of monocyte-derived macrophages and T lymphocytes (1,19). The cellular interactions in atherosclerosis are fundamentally not different from those in chronic inflammatory diseases such as RA(19). Macrophages and lymphocytes are abundant in the inflammatory synovium of patients with RA. Moreover, inflammatory mediators such as interleukin 1 (IL-1) and tumour necrosis factor (TNF), found in high concentrations in the blood of patients with RA, have profound effects on endothelial function, which is a main step in the development of atherosclerosis (1, 21).

Changes in atherosclerosis are responsible for increased stiffness of the wall in the affected arteries (6, 8). Parameters reflecting the elastic properties of the arterial wall such as distensibility and PWV may be affected early in the process of atherosclerosis (6, 8). Distensibility provides information on arterial elasticity at the measured site, while PWV is related to the average stiffness of an arterial segment over which the pulse wave travels between two measurement sites (7). In the present study, we assessed both the distensibility and PWV of the thoracic aorta and found decreased distensibility and increased PWV in patients compared to controls. Our results indicate increased stiffness of the aorta in patients with JIA and might be suggestive of early sub-clinical atherosclerosis.

In the present study the aortic distensibility decreased with age and the PWV increased with age in both patients and controls. Our results are in accordance with previous studies which demonstrated that the aortic stiffness increases with advancing age (9,22). This decrease in the arterial elasticity is consistent with the reduction in elastin and increase in collagen content of the arterial wall which are known to be age-related phenomena (23).

In the general population prospective studies have demonstrated that CRP predicts the future risk for cardiovascular disease (24,25). However, in adult

Table I. Aortic distensibility and pulse wave velocity (PWV) in the three subtypes of JIA.

	Oligoarticular	Polyarticular	Systemic
Age	14 (3.4 – 26.2)	14 (9.2 – 16.8)	12 (6.9 – 15.3)
Distensibility	9.7 (4.8 – 18.4)	11.6 (5.1 – 14.9)	10.3 (4.7 – 16.8)
PWV	3.1 (1.5 – 7.09)	3.2 (2.03 – 4.99)	3.5 (1.77 – 6)

Values are expressed as means (range).

patients with medium term RA, the common carotid artery intima-media thickness (IMT), a marker of generalised atherosclerosis, did not correlate with CRP nor with accumulated disease activity (26). This is in accordance with our results, since aortic distensibility and PWV did not correlate either with CRP or with accumulated disease activity. The results of the present study and previous studies (26) suggest that the atherosclerotic process in RA may not be directly associated with acute phase inflammation.

In patients with JIA, abnormalities in the lipid profile have been previously described (27, 28). In the present study aortic distensibility and PWV did not correlate with lipid variables. Our results probably suggest that increased aortic stiffness in JIA is not directly related to the lipid profile.

In our study treatment with corticosteroids did not affect the elastic properties of the thoracic aorta. These drugs in high doses have a recognized atherogenic effect through their effects on plasma lipids (1). Our JIA patients were on low-dose corticosteroid treatment. Moreover, as inflammation is implicated in atherosclerosis, cortisone may also have an anti-atherogenic effect (29).

Hyperhomocysteinemia has been associated with atheromatosis (1, 19, 21). Homocysteine plasma levels may be elevated in patients with RA(30,31). In this study all patients had normal homocysteine concentrations. Moreover, homocysteine plasma levels did not influence the aortic distensibility and PWV.

There are controversial data regarding the role of methotrexate (MTX) in the development of atherosclerosis in patients with RA. Landewe *et al.* (32) suggested that MTX may promote atherosclerosis in patients who already

have atherosclerotic vascular disease. The possible mechanism described was an increase in homocysteine plasma concentrations through the anti-folate effect of MTX (1). On the other hand, in a study on a larger cohort of RA patients Choi *et al.* (33) provided data suggesting that increased MTX use results in a substantial decrease in cardiovascular mortality. One probable explanation may be that MTX improves the mobility of patients and decreases systematic inflammation. According to our results, methotrexate treatment did not influence aortic distensibility and PWV.

In conclusion, we found increased aortic stiffness in patients with JIA using a non-invasive imaging method. These alterations in aortic elastic properties might suggest subclinical atherosclerosis. Physicians who provide medical care to patients with JIA should be aware of the probable future risk for atherosclerosis and monitor carefully aortic distensibility and PWV in their patients. In such cases phase contrast MR may be useful in patient follow-up.

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