Relationship between carotid intima-media thickness and arterial stiffness in children after Kawasaki disease

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Arch. Dis. Child. 2007;92;43-47; originally published online 4 Jul 2006;
doi:10.1136/adc.2006.096628

ORIGINAL ARTICLE

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Arch Dis Child 2007;**92**:43–47. doi: 10.1136/adc.2006.096628

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Accepted 26 June 2006
Published Online First 4 July 2006

Background: Evidence of premature atherosclerosis and systemic arterial stiffening in patients after Kawasaki disease is accumulating.
Aim: To test the hypothesis that carotid intima-media thickness (IMT), a surrogate marker of atherosclerosis, is associated with systemic arterial stiffness in children after Kawasaki disease.
Methods: A cohort of 72 patients was studied, comprising 26 patients with Kawasaki disease and coronary aneurysms (group I), 24 patients with Kawasaki disease and normal coronary arteries (group II) and 22 healthy age-matched children (group III). The carotid IMT, carotid artery stiffness index, brachioradial pulse wave velocity (PWV), fasting total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were determined and compared among the three groups.
Results: The carotid IMT was related to indices of arterial stiffness, and significant determinants of carotid IMT were identified by multivariate analysis. The mean (standard deviation (SD)) carotid IMT of both group I (0.41 (0.04) mm) and group II (0.39 (0.04) mm) was significantly greater than that of group III (0.36 (0.04) mm; $p<0.001$ and $p=0.008$, respectively). For the entire cohort, carotid IMT correlated positively with LDL cholesterol ($r=0.31$, $p=0.009$), carotid artery stiffness index ($r=0.40$, $p=0.001$) and brachioradial PWV ($r=0.28$, $p=0.016$), but not with age, body mass index, systemic blood pressure, and HDL and total cholesterol. Multiple linear regression analysis identified carotid artery stiffness index ($\beta=0.25$, $p=0.028$) and subject grouping ($\beta=-0.39$, $p=0.001$; model $R^2=0.29$) as significant correlates of carotid IMT.
Conclusion: The increased carotid IMT in children after Kawasaki disease is associated with systemic arterial stiffening.

There is increasing evidence to suggest that children with a history of Kawasaki disease might be predisposed to premature atherosclerosis.[1–4] Endothelial dysfunction, a key event of atherosclerosis, has been seen in children after Kawasaki disease, regardless of their having coronary artery lesions.[1] We and others have further shown the proatherogenic changes in the lipid profile[2–4] of these patients. Noto *et al*[5] found an increase in carotid intima-media thickness (IMT), a surrogate marker of atherosclerosis, in both children[6] and adults[7] late after the acute disease in patients with coronary artery lesions. Stiffening of the central and peripheral arteries has also been found in patients with Kawasaki disease.[4 5 8 9] Although traditionally regarded as part of the normal ageing process, arterial stiffening may precede clinical disease and predict a higher risk for developing atherosclerosis, hypertension and stroke in adults.[10] Previous studies examining the association between arterial stiffness and atherosclerosis in high-risk adults have shown a significant positive relationship.[11–14] We hypothesised that carotid IMT is associated with systemic arterial stiffness in children after Kawasaki disease. Accordingly, the objective of our study was to test this hypothesis by examining the association between carotid IMT, a marker of atherosclerosis, and indices of carotid and brachioradial artery stiffness in these patients.

METHODS

Participants

Patients with a history of Kawasaki disease were recruited from the Paediatric Cardiac Clinic, Grantham Hospital, Hong Kong, China. All recruited patients had normal left ventricular shortening fraction and absence of valvar incompetence as documented by serial echocardiographic studies. Healthy age-matched participants, who were children previously discharged from our clinic with a diagnosis of functional heart murmur and their healthy siblings, were recruited as controls. The institutional ethics committee approved the study and parents of all participants gave written, informed consent.

We reviewed the case records of the patients and collected the following data: interval from disease onset to time of study, coronary artery lesions, cardiac symptoms and drugs at the time of study. Coronary aneurysms were documented by serial two-dimensional echocardiography. The participants were categorised into three groups for comparisons: group I, patients with persistent or regressed coronary aneurysms; group II, patients who never had echocardiographically documented coronary artery lesions; and group III, healthy controls.

The participants were examined after an overnight fast. The body weight and height were measured, and the body mass index (weight (kg)/height^2 (m^2)) was calculated accordingly. Blood pressure in the right arm was measured twice using an automatic oscillometric device (Dinamap, Critikon, Tampa, Florida, USA), with the participants in the seated position after at least 10 min of rest. The average of the two blood pressure readings was taken.

Assessment of arterial stiffness

The carotid artery stiffness was assessed by calculating the stiffness index as reported previously.[15 16] Briefly, a 7–15 MHz linear-array transducer, interfaced to a Hewlett-Packard Sonos 5500 ultrasound machine (Hewlett-Packard Corp, Andover, MA, USA), was used to image the right carotid artery at about 1 cm proximal to the carotid bifurcation. The systolic and diastolic diameters were measured between the intima of the

Abbreviations: HDL, high-density lipoprotein; IMT, intima–media thickness; LDL, low-density lipoprotein; PWV, pulse-wave velocity

near and far walls. Three measurements each of systolic and diastolic diameters were averaged for the calculation of stiffness index according to the formula:

$$\ln (SBP/DBP)/(\delta D/D),$$

where ln denotes natural logarithm, SBP systolic blood pressure, DBP diastolic blood pressure, δD the difference between systolic and diastolic diameters, and D the mean diameter.

The brachioradial artery stiffness was assessed by measuring the pulse-wave velocity (PWV), using the previously reported photoplethysmographic technique.[17] PWV is related to the square root of elastic modulus according to the Moens–Korteweg equation.[18] Hence, the stiffer the artery, the faster the PWV. The transit time required for the pulse to travel from the brachial artery at the elbow to the radial artery at the wrist was determined from the time delay between the foot of the corresponding brachial and radial pulse waves. The average of three readings was taken. PWV was calculated by dividing the surface distance between the two sites of pulse wave recording by the transit time.

Carotid IMT

The right carotid artery was similarly imaged using the linear array transducer as aforementioned at about 1 cm proximal to the carotid bifurcation. The IMT of the common carotid artery far wall was measured using the electronic callipers of the ultrasound machine as described previously.[5] All the measurements were carried out by a single investigator (SJW), blinded to the status of the participants and the stiffness indices. The average of three measurements was used for subsequent analyses.

Blood investigations

The fasting total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels were determined. Plasma total cholesterol level was determined enzymatically using a Hitachi 912 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). HDL cholesterol was measured using a homogeneous method with polyethylene glycol-modified enzymes and sulphated α-cyclodextrin, and LDL cholesterol was calculated by the Friedewald equation.

Data analysis

Data are presented as mean (SD). One-way analysis of variance was used to compare differences in the variables among the three groups, with retrospective comparisons using the Bonferroni test. For categorical variables, χ^2 test was carried out. Pearson's correlation analysis was used to assess for correlations between carotid IMT and demographic variables, systemic blood pressure and indices of arterial stiffness. Stepwise multiple linear regression was used to identify significant determinants of carotid IMT. Values of $p<0.05$ were considered to be significant. All statistical analyses were carried out using SPSS V.11.5.

RESULTS

Participants

We studied a total of 72 participants. Group I comprised 26 patients with Kawasaki disease, half of whom had persistent coronary aneurysms, whereas group II comprised 24 patients with Kawasaki disease. None had symptoms of myocardial ischaemia and none required coronary artery interventions. All but five of the patients with Kawasaki disease had received intravenous immunoglobulin treatment during the acute phase of illness and 13 were maintained on long-term oral low-dose aspirin treatment. Group III comprised 22 age-matched controls.

Table 1 summarises the demographic variables, systemic blood pressure and lipid profiles of the participants. The three groups did not differ markedly with regard to age at the time of study, sex distribution, body mass index, systemic blood pressure, total cholesterol level and HDL cholesterol level. However, group I patients had higher LDL cholesterol level, as reported previously.[4]

Arterial stiffness

The carotid artery stiffness index ($p = 0.004$) and brachioradial PWV ($p = 0.011$) differed significantly among the three groups. The differences remained significant even after adjusting for the differences in LDL cholesterol among groups. The mean (SD) stiffness index of group I, II and III was 4.72 (1.20), 4.22 (0.64) and 3.77 (0.92), respectively. The respective mean (SD) brachioradial PWV was 7.22 (1.67), 6.73 (1.88), and 5.77 (1.25) m/s. Post-hoc analyses showed that group I had a significantly greater stiffness index ($p = 0.003$) and faster brachioradial PWV ($p = 0.009$) than group III. Therefore, a

Table 1 Demographic data, blood pressure and lipid profiles of participants in the three groups

	Group I (n = 26)	Group II (n = 24)	Group III (n = 22)	p Value
Age at study (years)	8.6 (2.8)	8.6 (3.3)	9.5 (2.5)	0.52
Age at diagnosis of KD (years)	1.5 (1.7)	2.7 (2.6)	–	0.10
Interval from diagnosis to time of study (years)	7.4 (3.5)	5.8 (2.1)	–	0.09
Sex (male:female)	17:9	16:8	14:8	0.98
BMI (kg/m^2)	16.9 (2.7)	15.8 (2.0)	16.9 (3.7)	0.34
SBP (mm Hg)	107 (14)	107 (8)	107 (11)	0.99
DBP (mm Hg)	58 (9)	58 (5)	57 (7)	0.97
Total cholesterol (mmol/l)	4.5 (0.9)	4.4 (0.9)	4.1 (0.7)	0.22
HDL cholesterol (mmol/l)	1.4±(0.3)	1.5 (0.3)	1.5 (0.4)	0.29
LDL cholesterol (mmol/l)	2.8 (0.8)	2.6 (0.8)	2.2 (0.6)	0.02*

BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; KD, Kawasaki disease; LDL, low-density lipoprotein; SBP, systolic blood pressure; –, no data available.
Values are mean (SD) unless otherwise specified.
*Significant p value.

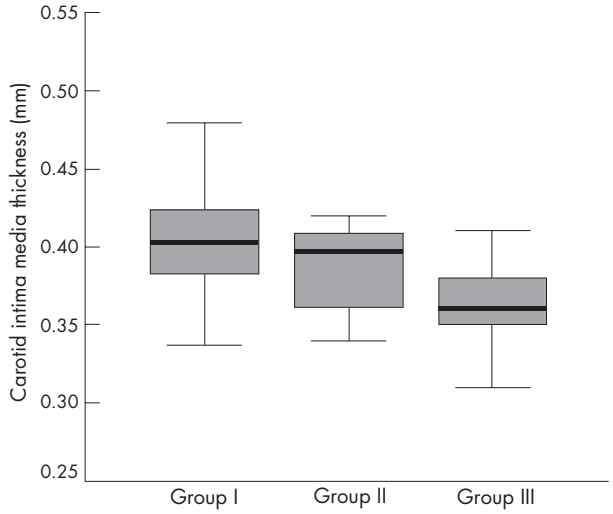

Figure 1 Box plots showing the distribution of carotid intima-media thickness in the three groups of participants. The thick black line within each box represents the median in each group.

dose–response relationship between the degree of coronary artery involvement and arterial stiffness indices was hence suggested.

Carotid IMT

The carotid IMT similarly differed significantly among the three groups ($p<0.001$; fig 1). Post-hoc analyses showed that the mean (SD) carotid IMT of group I (0.41 (0.04) mm, $p<0.001$) and group II (0.39 (0.04) mm, $p = 0.008$) was significantly greater than that of group III (0.36 (0.04) mm).

For the entire cohort, carotid IMT correlated positively with LDL cholesterol ($r = 0.31$, $p = 0.009$), carotid artery stiffness index ($r = 0.40$, $p = 0.001$) and brachioradial PWV ($r = 0.28$, $p = 0.016$; fig 2), but not with age, body mass index, systemic blood pressure, or HDL and total cholesterol. Multiple stepwise linear regression analysis of the entire cohort was used to identify significant correlates of carotid IMT. The dependent variables included were age, sex, body mass index, subject grouping, systolic and diastolic blood pressures, total cholesterol, HDL cholesterol, LDL cholesterol, carotid artery stiffness index and brachioradial PWV. Significant correlates were subject grouping ($\beta = -0.39$, $p = 0.001$) and carotid artery stiffness index ($\beta = 0.25$, $p = 0.028$; model $R^2 = 0.29$). When only the patients (group I and II) were analysed, with addition of duration since onset of Kawasaki disease as a covariate into the multivariate model, total cholesterol level ($\beta = 0.29$, $p = 0.03$) and carotid artery stiffness index ($\beta = 0.53$, $p<0.001$) (model $R^2 = 0.35$) were found to be significant.

DISCUSSION

Increase in carotid IMT has been reported in patients with Kawasaki disease and coronary artery lesions.[5] Our study extends this finding to patients without documented coronary sequelae. Furthermore, to our knowledge, this is the first study to show a significant association between carotid IMT and systemic arterial stiffness in children after Kawasaki disease. After adjustment of the potential confounding influence of age, sex, systemic blood pressure and serum cholesterol levels, the significant correlates of carotid IMT in patients with Kawasaki disease are carotid artery stiffness index and total cholesterol level.

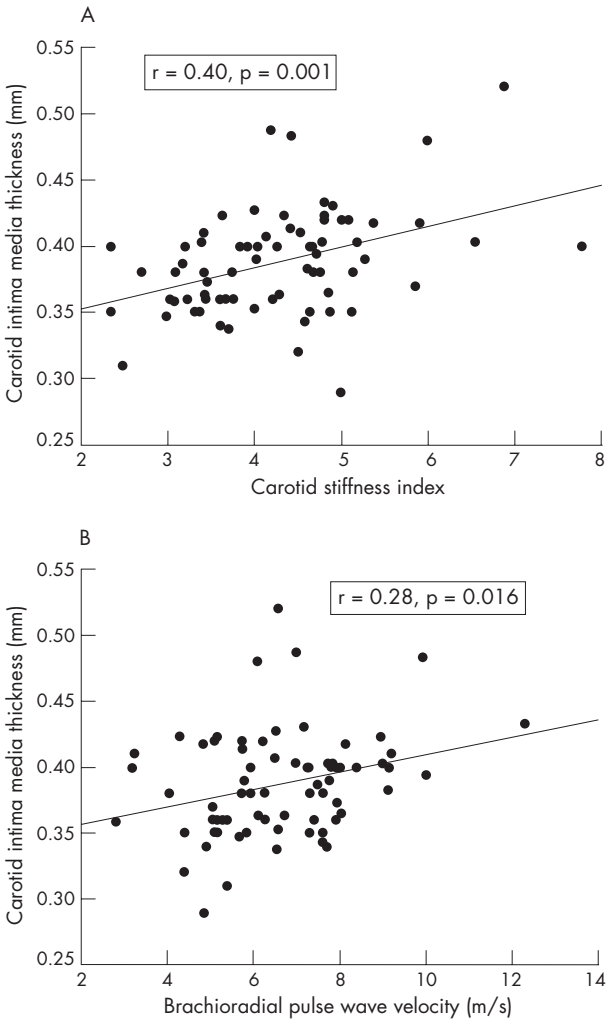

Figure 2 Scatter plots showing a positive correlation between carotid intima–media thickness and (a) carotid stiffness index, and (b) brachioradial pulse-wave velocity.

Carotid IMT has been regarded as a valid surrogate marker of atherosclerosis in adults[7] and is associated with cardiovascular events.[19 20] In high-risk children with obesity,[21] hypercholesterolaemia,[22] type 1 diabetes mellitus[23] and a family history of premature myocardial infarction,[24] carotid intima-media thickening has likewise been seen. In children with coronary aneurysms complicating Kawasaki disease, Noto *et al*[5] reported carotid intima–media thickening, although patients without coronary artery lesions were not included in their study. A recent Japanese study,[25] however, reported no differences in carotid IMT among patients with varying severity of coronary artery lesions and between patients and controls. Nonetheless, these findings have to be interpreted with caution as the number of patients studied in each group is too small to provide adequate statistical power, and controls were significantly older than patients. As age-dependent physiological thickening of the carotid IMT begins in childhood,[26] a comparison of the findings with those of age-matched controls is essential.

Our finding of carotid intima-media thickening not only in patients with Kawasaki disease but also in those without coronary artery lesions is perhaps not surprising. Even in regressed coronary artery aneurysms and angiographically normal coronary arterial segments, long-term functional

abnormalities have been described.[27] Systemic arterial endothelial dysfunction has also been shown years after Kawasaki disease, even in patients without coronary artery involvement.[1] Fatal cases of Kawasaki disease, related to extensive fibrointimal thickening of the coronary arterial wall, occurring years after apparent resolution of vascular inflammation and in the absence of early detectable coronary artery abnormalities, have also been reported.[28] Patients without coronary artery lesions do not, therefore, seem to be immune from the hypothesised risk of premature atherosclerosis.

Stiffening of the aorta,[8] carotid artery[5] and brachioradial artery[4] have been reported in children after Kawasaki disease. Senzaki *et al*[9] measured the aortic input impedance during cardiac catheterisation in patients with Kawasaki disease and found increased characteristic impedance, lower total peripheral arterial compliance and greater indices of arterial wave reflection, regardless of the persistence of coronary artery lesions. Their findings provide further evidence of central and peripheral arterial stiffening after Kawasaki disease. Although the underlying mechanisms of the disease remain speculative, arterial stiffening has been attributed to structural changes and the subsequent reparative process during the acute illness,[29] and changes in the vascular tone secondary to endothelial dysfunction.[1] Our group has further provided evidence of ongoing low-grade inflammation late after the acute phase of Kawasaki disease, which may have a role in increasing systemic arterial stiffness.[15]

The finding of an association between increased carotid IMT and systemic arterial stiffness in this study is consistent with previous studies in animal models,[30] postmortem specimens,[11] adults with various levels of cardiovascular risk,[14 31] patients with hypertension[13] and adults with atheromatous plaques in the thoracic aorta owing to various pathologies.[12] Results of other studies are nonetheless conflicting.[32–34] The recent evidence suggesting that IMT may reflect atherosclerosis only beyond a certain level[35] may perhaps partly explain the controversy. Alternatively, the association may not be as obvious in early changes as that in advanced atherosclerotic changes in the arterial wall.[36] In young adults, the weak positive association becomes stronger in patients with a worse cardiovascular risk profile.[32] The adverse cardiovascular risk profile in patients with Kawasaki disease may perhaps have some significance in this regard.

The coexistence of and association between a marker of atherosclerosis, the carotid IMT, and systemic arterial stiffness in this study may partly reflect common aetiological factors relating to Kawasaki disease. Although these may be independent processes that reflect two separate entities of vascular damage in Kawasaki disease, several lines of evidence favour the hypothesis of a self-perpetuating process. Experimental studies in monkeys fed on an atherogenic diet,[30] spontaneously hypercholesterolaemic rabbits,[37] and LDL-receptor deficient hypercholesterolaemic rabbits[38] suggest that atherosclerosis leads to stiffening of the aorta. Stiffening of the arterial wall, on the other hand, may increase intraluminal stress secondary to an increase in pulse pressure,[39] which may predispose to vascular damage and atherosclerosis. Increased pulse pressure has indeed been shown to augment atherogenesis in primate models.[40] It is intriguing, therefore, to find that only local carotid artery stiffness, rather than brachioradial artery stiffness, is a significant correlate of carotid IMT by multivariate analysis. The possibility of establishing a feedback loop owing to structural and functional abnormalities of the arteries in patients with Kawasaki disease may be hypothesised, although further longitudinal studies are undoubtedly needed to determine the temporal sequence of carotid intima-media thickening and arterial stiffening after Kawasaki disease.

What is already known on the topic

- Increased carotid intima-media thickness has been reported in patients with Kawasaki disease and coronary artery lesions.
- Central and peripheral arterial stiffening occurs in children after Kawasaki disease.

What this study adds

- Carotid intima-media thickness (IMT) is increased even in patients with Kawasaki disease without coronary sequelae.
- A significant association is found between carotid IMT and systemic arterial stiffness in children after Kawasaki disease.

Even in patients without coronary artery lesions, a proatherogenic lipid profile,[4] endothelial dysfunction,[1] systemic arterial stiffening[4 9] and increased carotid IMT have been found. Ongoing counselling on cardiovascular risk factor reduction is therefore important. Periodic assessment of the cardiovascular risk factors every 3–5 years has been suggested for this group of patients with Kawasaki disease in the recently revised American Heart Association recommendations.[41] Whether strategies to reduce arterial stiffness and ways to improve endothelial function would benefit patients with Kawasaki disease in the long term are topics for further research.

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Competing interests: None declared.

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