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Objectives: To test the hypothesis that low grade inflammation persists after the acute phase and affects arterial stiffness in children with a history of Kawasaki disease.

Design and patients: A cohort of 106 children was studied, which comprised 43 patients with Kawasaki disease with coronary aneurysms (group I), 28 patients with Kawasaki disease with normal coronary arteries (group II), and 35 healthy age matched children (group III). Their systemic blood pressure, fasting cholesterol concentrations, serum high sensitivity C reactive protein (hs-CRP) concentrations, and carotid artery stiffness index were compared. Significant determinants of serum hs-CRP concentration and carotid artery stiffness were identified and the relation between hs-CRP concentration and arterial stiffness was investigated.

Setting: Tertiary paediatric cardiac centre.

Results: Serum hs-CRP concentration of group I patients (median 0.39 mg/l, interquartile range 0.28–0.65 mg/l) was significantly greater than that of group II (median 0.24 mg/l, interquartile range 0.17–0.29 mg/l, $p < 0.001$) and of group III patients (median 0.25 mg/l, interquartile range 0.18–0.40 mg/l, $p < 0.01$). Likewise, carotid artery stiffness index of group I patients (mean (SD) 5.07 (1.11)) was significantly greater than that of group II (4.27 (0.83), $p = 0.002$), and of group III patients (4.24 (0.86), $p = 0.001$). For the entire cohort, the carotid artery stiffness index correlated positively with log serum hs-CRP concentration ($r = 0.24$, $p = 0.013$). In multiple linear regression analysis, age (standardised $\beta = 0.22$, $p = 0.02$), systolic blood pressure (standardised $\beta = 0.28$, $p = 0.01$), log serum hs-CRP concentration (standardised $\beta = 0.21$, $p = 0.017$), and patient grouping (standardised $\beta = -0.36$, $p < 0.001$) were all independently associated with the carotid artery stiffness index.

Conclusions: These findings support the possibility of ongoing low grade inflammation late after the acute phase of Kawasaki disease in patients with coronary aneurysms. Furthermore, this low grade inflammation may have a role in increasing systemic arterial stiffness.

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Kawasaki disease, a systemic vasculitis with predilection for Asian children, is the most common acquired heart disease in children in developed countries.[1] The sequelae of inflammation involving coronary and other medium sized muscular arteries in the acute phase of Kawasaki disease have been well documented.[2–4] In the absence of significant coronary artery complications, long term morbidity has generally been regarded as minimal.[2] Nonetheless, fatal cases of Kawasaki disease that occurred years after apparent resolution of vascular inflammation and in the absence of early detectable coronary artery abnormalities have recently been reported.[5] Histological examination showed extensive fibrointimal thickening and infiltration of lymphocytes and plasma cells in the coronary arterial walls.[5] These findings suggest that chronic low grade arterial inflammation is possible even years after resolution of the acute phase of Kawasaki disease.

Recently, there has been a surge of studies of adults showing a direct association between slightly increased baseline high sensitivity C reactive protein (hs-CRP) serum concentrations and the risk of developing cardiovascular disease.[6–8] While CRP has traditionally been regarded as merely a marker of inflammation, recent evidence suggests that it may contribute directly to a proinflammatory state and pathogenesis of vascular damage.[9–12] Whether serum CRP concentration remains slightly increased late after Kawasaki disease, as a reflection of chronic low grade inflammation, has not been determined, however.

Evidence of systemic arterial dysfunction late after Kawasaki disease, on the other hand, is accumulating. Dhillon and colleagues[13] have shown abnormalities of brachial artery endothelial function years after resolution of acute Kawasaki disease, even in patients without detectable early coronary artery involvement. Our group has further reported that the stiffness of peripheral conduit arteries is increased in patients who did not receive immunoglobulin within 10 days of disease onset.[14] Recently, increased carotid artery stiffness has also been shown in patients who had associated coronary aneurysms.[15]

Given the preliminary evidence of late systemic artery dysfunction in Kawasaki disease and a possible link between chronic low grade inflammation and the risk of developing cardiovascular disease, we hypothesised that low grade inflammation persists for years after resolution of the acute phase of Kawasaki disease and that this inflammation may be associated with abnormal systemic artery function. To test this hypothesis, we compared the serum hs-CRP concentrations in children and adolescents with a history of Kawasaki disease with those in age matched healthy children and further determined the relation between serum hs-CRP concentration and carotid artery stiffness.

PATIENTS AND METHODS
Patients and design
Patients with a history of Kawasaki disease were recruited from the paediatric cardiac clinic of Grantham Hospital. The

following data were retrieved from their clinical records: age and symptoms at presentation, sex, use of intravenous immunoglobulin during the acute phase, coronary artery complications, current medications, and duration from onset of disease to the time of the study. Patients who had Kawasaki disease within 12 months of the study were excluded to minimise a potential confounding influence relating to subacute inflammation.[16] Healthy children matched to the mean age of patients with Kawasaki disease were recruited as controls. The institutional ethics committee approved the study and parents of all subjects gave written, informed consent.

The participants were categorised into three groups for comparisons. Group I comprised patients with Kawasaki disease and a history of documented coronary artery aneurysms; group II comprised patients without a history of coronary artery aneurysms; and group III comprised healthy age matched control patients. Coronary artery aneurysms were documented by serial two dimensional echocardiographic studies that were performed at the second week of illness and then at one, three, six, and 12 months. Patients with persistent aneurysms were assessed by echocardiography every six to 12 months thereafter.

All participants attended the study after an overnight fast. Body weight and height were measured and body mass index was calculated accordingly. All children rested for at least 15 minutes before blood pressure and cardiovascular assessments. Blood pressure in the right arm was measured twice with an automated oscillometric device (Dinamap, Critikon, Tampa, Florida, USA) and the two readings were averaged. Carotid artery stiffness was assessed as described below. Venous blood was then withdrawn from all participants for measurement of fasting cholesterol and hs-CRP concentrations.

Measurement of carotid artery stiffness

Carotid artery stiffness was assessed by calculating the stiffness index.[17] A 7–15 MHz linear array transducer interfaced to a Sonos 5500 ultrasound machine (Hewlett Packard, Andover, Massachusetts, USA) was used to image the right carotid artery at about 1 cm proximal to the carotid bifurcation. The diameter was measured between the intima of the near and far walls, perpendicular to the course of the artery. The maximum diameter at systole and the minimum diameter at end diastole, as defined by the R wave of the ECG, were measured. Three measurements each of systolic and diastolic diameters were averaged for calculation of the stiffness index according to the formula $\ln (SBP/DBP)/(\delta D/D)$,[17] where SBP is systolic blood pressure, DBP is diastolic blood pressure, δD is the difference between systolic and diastolic diameters, and D is the mean diameter. The intraobserver variability for measurement of systolic and diastolic diameters, as determined from the mean and SD of differences in two consecutive results from 20 studies, were −0.01 (0.18) mm and 0.00 (0.18) mm, respectively.

Measurement of cholesterol and hs-CRP concentrations

Plasma total cholesterol concentration was determined enzymatically on a Hitachi 912 analyser (Roche Diagnostics GmbH, Mannheim, Germany). High density lipoprotein (HDL) cholesterol was measured by a homogeneous method with polyethylene glycol modified enzymes and sulfated α cyclodextrin. Low density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation. The CRP was measured with a highly sensitive assay, which is a particle enhanced immunoturbidimetric assay consisting of an anti-CRP monoclonal antibody coupled to latex microparticles (Roche Diagnostics). The assay is standardised against a CRM 470 reference preparation for proteins in human serum and has a functional sensitivity of 0.1 mg/l.

Statistical analysis

Data are presented as mean (SD) and median (range) as appropriate. To compare the differences between groups, one way analysis of variance and post hoc Tukey test were used for parametric variables, Kruskal-Wallis test with post hoc comparison by Dunn's multiple comparison test for non-parametric variables, and χ^2 test for categorical variables. For comparison of two groups of non-parametric variables, the Mann-Whitney U test was used. As CRP concentrations had a skewed distribution, logarithmically transformed CRP concentrations were used in linear regression analyses. Furthermore, CRP concentrations in each of the groups were expressed as median and interquartile range. Stepwise multiple linear regression analyses of the entire cohort were used to identify significant determinants of serum CRP concentration and carotid artery stiffness. The groups of patients were entered as dummy variables (1 for group I, 2 for group II, and 3 for group III). Within the groups with Kawasaki disease (groups I and II), Spearman's correlation analysis was used to assess for a possible relation between CRP concentrations (logarithmically transformed) and the time since the acute illness. Significance was defined as a $p < 0.05$. All statistical analyses were done with SPSS version 10.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Participants

A total of 106 participants were studied. Group I comprised 43 patients, of whom 24 had persistent small coronary aneurysms, two had giant aneurysms, and 17 had regressed aneurysms. None had symptoms of myocardial ischaemia and none required coronary artery interventions. Group II comprised 28 patients with Kawasaki disease but without documented coronary artery lesions. Of the total of 71 patients with Kawasaki disease, all but five had received intravenous immunoglobulin during the acute phase of illness and 32 were continuing to take long term oral low dose aspirin. The patients were studied at a median time interval of 7.2 years (range 1.0–16.6 years) from onset of disease. Group III comprised 35 healthy control participants. Table 1 summarises the demographic, haemodynamic, and lipid profiles of all three groups. The three groups did not differ significantly with regard to age at presentation, age at the time of study, sex distribution, body mass index, systemic blood pressure, and total cholesterol concentration. However, in agreement with previous reports,[18] HDL cholesterol was significantly lower in group I patients.

Serum hs-CRP concentrations

The serum hs-CRP concentrations had a positively skewed distribution. Only one of the patients had an hs-CRP concentration of less than the detectable limit, which was assigned a value of 0.05 mg/l.

The hs-CRP concentration of group I patients (median 0.39 mg/l, interquartile range 0.28–0.65 mg/l) was significantly greater than that of group II (median 0.24, interquartile range 0.17–0.29 mg/l, $p < 0.001$) and of group III patients (median 0.25 mg/l, interquartile range 0.18–0.40 mg/l, $p < 0.01$) (fig 1). There was, however, no significant difference in hs-CRP concentrations between group II and group III ($p > 0.05$). Within group I, patients with persistent coronary artery aneurysms had hs-CRP concentrations (median 0.36, interquartile range 0.24–0.53) similar to those with regressed aneurysms (median 0.36, interquartile range 0.24–0.69, $p = 0.65$).

Table 1 Demographic, haemodynamic, and lipid profiles of the three groups

	Group I (n = 43)	Group II (n = 28)	Group III (n = 35)	p Value
Age at study (years)	10.2 (4.1)	9.7 (3.2)	10.3 (3.6)	0.72
Age at diagnosis of Kawasaki disease (years)	1.3 (0.2–7.3)	1.8 (0.2–10.7)	NA	0.27
Interval from diagnosis to time of study (years)	7.8 (1–16.6)	6.9 (1.1–13.2)	NA	0.11
Sex (male:female)	28:15	19:9	25:10	0.84
Body mass index (kg/m^2)	17.5 (2.8)	16.9 (2.8)	17.3 (3.3)	0.14
Systolic blood pressure (mm Hg)	120 (14)	107 (8)	109 (10)	0.53
Diastolic blood pressure (mm Hg)	58 (9)	58 (5)	57 (7)	0.61
Total cholesterol (mmol/l)	4.36 (0.81)	4.43 (0.84)	4.21 (0.78)	0.54
HDL cholesterol (mmol/l)	1.31 (0.25)	1.46 (0.28)	1.46 (0.33)	0.035*
LDL cholesterol (mmol/l)	2.65 (0.69)	2.64 (0.75)	2.34 (0.71)	0.13

Data are mean (SD) or mean (range).
*Significant.
HDL, high density lipoprotein; LDL, low density lipoprotein; NA, not applicable.

Multiple linear regression of the entire cohort of 106 patients was performed to identify significant determinants of serum hs-CRP concentrations. The following dependent variables were tested: age, sex, body mass index, SBP, DBP, HDL and LDL cholesterol concentrations, and patient grouping. Significant determinants were body mass index (standardised β = 0.42, p < 0.001) and patient grouping (standardised β = −0.19, p = 0.035). Thus, patients with coronary artery aneurysms had significantly higher hs-CRP concentrations even after adjustments of age, sex, body mass index, SBP, and HDL cholesterol, all of which have been found to correlate with baseline hs-CRP concentrations in healthy children.[19] There was, however, no correlation between hs-CRP concentrations and the time since the acute illness among patients (p = 0.60).

Carotid artery stiffness

The mean (SD) carotid artery stiffness index of group I (5.07 (1.11)) was significantly greater than that of group II (4.27 (0.83), p = 0.002) and of group III patients (4.24 (0.86), p = 0.001). Importantly, there was a significant positive correlation between carotid artery stiffness index and log serum hs-CRP concentration (r = 0.24, p = 0.013) (fig 2).

Multiple linear regression of the entire cohort was similarly performed to identify significant determinants of carotid artery stiffness index. Dependent variables that were entered into the multivariate model were age, sex, body mass index, SBP, DBP, HDL, and LDL cholesterol concentrations, serum hs-CRP concentrations, and patient grouping. Significant determinants were age (standardised β = 0.22, p = 0.02), SBP (standardised β = 0.28, p = 0.01), serum hs-CRP
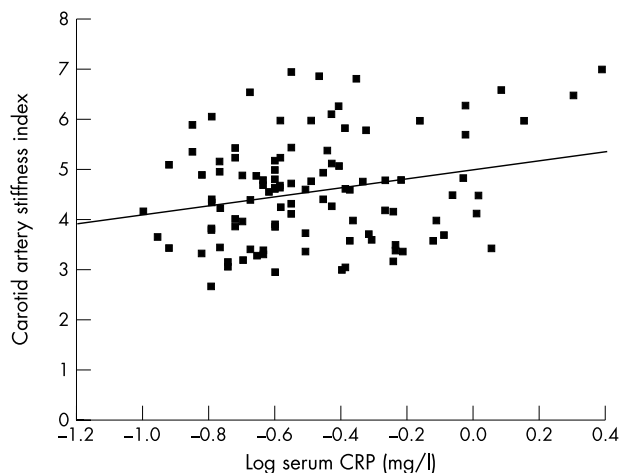

Figure 2 Scatter plot showing a positive correlation between serum CRP concentration (logarithmically transformed) and carotid artery stiffness index.

concentrations (standardised β = 0.21, p = 0.017), and patient grouping (standardised β = −0.36, p < 0.001).

DISCUSSION

This study showed that serum hs-CRP concentrations are significantly increased in children and adolescents with a history of Kawasaki disease complicated by coronary aneurysm formation. Importantly, there is a positive relation between CRP concentration and carotid artery stiffness. Our findings provide the first evidence that chronic low grade inflammation may continue after the acute phase of Kawasaki disease and perhaps have a role in alteration of arterial function.

While a significant increase of CRP concentration is characteristic during the acute phase of Kawasaki disease, the baseline hs-CRP concentration and its significance in the late phase of the disease have not been determined. Recent studies of adults have shown a direct association between slightly increased baseline hs-CRP concentrations and the risk of developing cardiovascular disease.[6–8] Furthermore, increased concentrations of hs-CRP have been found to predict recurrent ischaemia, myocardial ischaemia, and sudden death among adult patients with multiple risk factors for coronary artery disease.[20 21] In children with Kawasaki disease, at sites of persistent and even regressed coronary artery aneurysms, structural alterations with intimal thickening and smooth muscle cell proliferation and functional alterations as characterised by arterial stiffness and endothelial dysfunction are well documented.[3 4] Furthermore, reports
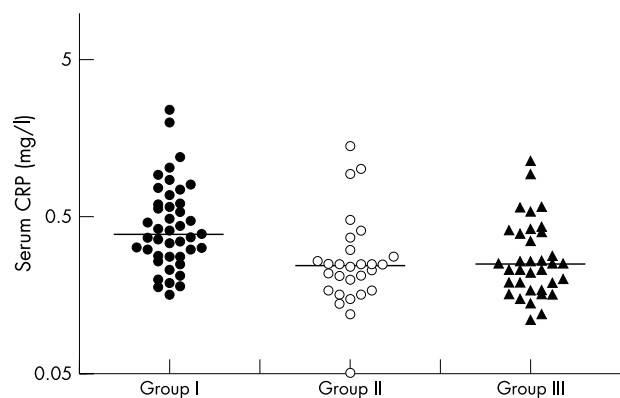

Figure 1 Distribution of serum C reactive protein (CRP) concentrations (on a log scale) in the three groups of patients. The horizontal lines represent the medians in each of the groups.

are accumulating of coronary artery sequelae in patients with early Kawasaki disease leading to ischaemic heart disease in young adults.[22][23] Our findings of increased baseline hs-CRP concentrations in children and adolescents with coronary artery sequelae late after the acute phase of Kawasaki disease may therefore have important implications.

Increased hs-CRP concentrations in the presence of associated coronary aneurysms, whether persistent or regressed, is probably a reflection of continuing low grade vasculitis. This corroborates with the previously reported histological findings of infiltration of lymphocytes and plasma cells in the arterial walls of patients who died years after apparent resolution of the acute vascular inflammation.[5] As Takahashi[24] suggested, while intravenous immunoglobulin has been effective in extinguishing the fire during the acute stage of Kawasaki disease, it might have failed to snuff out the smouldering vasculitis in the later stage of the disease. Our findings support this proposition and further suggest that this smouldering vasculitis may perhaps play a part in altering arterial function.

Increased carotid stiffness in the absence of major alteration of the lipid profile has recently been described by Noto and colleagues[15] in a group of 20 adolescents with Kawasaki disease and coronary artery lesions. Patients without coronary artery complications were, however, not included in their study. Our findings corroborate with theirs and further show that patients without coronary artery lesions have normal carotid artery stiffness. The underlying mechanisms accounting for the increase in carotid artery stiffness remain speculative. Nonetheless, the fact that patient status is one of the significant determinants of stiffness suggests that diffuse vasculitis, involving both coronary and non-coronary arteries, changes the arterial wall structure and hence its elastic modulus may be one of the possible mechanisms. However, there is no documented evidence of a histological difference between sick and healthy people.

On the other hand, an additional novel finding of the present study is the significant positive correlation between serum hs-CRP concentrations and arterial stiffness. In adults, increased hs-CRP concentrations have been found to be associated with endothelial dysfunction in patients with coronary artery disease.[10] In vitro studies have further shown that CRP induces adhesion molecule expression in human endothelial cells in the presence of serum.[25] In the only available study among healthy children of the impact of increased hs-CRP concentrations on arterial changes,[26] increased hs-CRP concentrations were found to be associated with increased intima–media thickness and likewise endothelial dysfunction. Indeed, increased intima–media thickness measured by carotid ultrasonography has been found in patients with a history of Kawasaki disease and coronary aneurysms.[15] Thus, our findings together with those of the other groups may tempt one to speculate that increased serum hs-CRP concentrations may predispose to structural and functional changes of arteries in these patients. Nonetheless, in children and adolescents who do not have much of an atherosclerotic burden, whether hs-CRP is indeed a risk factor or a risk marker requires further clarification.[27]

A number of limitations may deserve comment. Firstly, low dose aspirin administered to patients with coronary aneurysms may potentially affect serum hs-CRP concentrations. However, the findings of previous studies of adults with coronary artery disease and healthy adults are controversial.[28–30] Nonetheless, in the positive studies reported so far,[28][29] the effect of low dose aspirin is lowering of serum hs-CRP concentrations. Thus, in our group I patients, if aspirin were to have any influence on their serum hs-CRP concentrations, the chance of detecting a significant difference

between groups would be minimised rather than exaggerated. Secondly, it may be argued that, in the strictest sense, group I comprised two subsets of patients, as defined by the persistence or regression of coronary artery aneurysm. However, the similar morphological and functional coronary artery abnormalities as reported previously[4] suggest that these patients share similar features of arterial dysfunction. It is therefore justified to combine the two subsets into a single group for analysis. Indeed, the hs-CRP concentrations were similar between the two subgroups. Thirdly, 37% (26 of 71) of our patients with a history of Kawasaki disease had persistent coronary aneurysms, a proportion much higher than that expected after administration of intravenous immunoglobulin. This is likely to be related to tertiary referral bias. Nonetheless, this provides an opportunity to further stratify the patients for comparison of differences in hs-CRP concentrations and arterial stiffness in different subgroups.

In summary, our findings support the possibility of ongoing low grade inflammation late after the acute phase of Kawasaki disease among patients with coronary aneurysms. Furthermore, this low grade inflammation may play a part in late systemic artery dysfunction. Suppression of this chronic inflammatory process may be a new target for intervention, which may perhaps improve arterial function in the long term.

ACKNOWLEDGEMENTS

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IMAGES IN CARDIOLOGY ....

Homozygous familial hyperlipidaemia presenting as severe aortic stenosis and unstable angina

A 51 year old man with a known history of homozygous familial hyperlipidaemia on regular plasmapheresis, presented with unstable angina. Examination of the precordium revealed a harsh ejection systolic murmur grade 4/6 over the aortic area with radiation to the neck. An ECG showed Q waves over the inferior leads, and sinus rhythm with left ventricular strain pattern. A coronary angiogram showed chronic total occlusion of the right coronary artery and minor disease over the left coronary vessels. Fluoroscopy showed dense calcification affecting the aortic valves and proximal portion of the ascending aorta. Transoesophageal echocardiography demonstrated severely calcified, immobile aortic valve trileaflets with valve area by planimetry of ~0.8 cm². A contrast enhanced multislice computed tomographic (CT) scan was performed to assess the extent of calcification of the aorta before referral for surgery (panels A–C: sagittal CT and corresponding three dimensional reconstruction images).
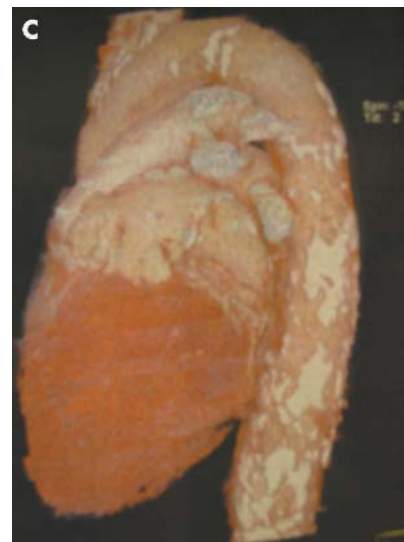
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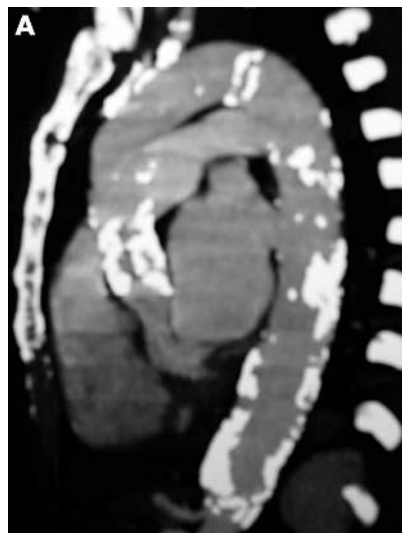
Sagittal view of the aorta—note calcified atherosclerotic plaques extending from the aortic root upwards in the ascending thoracic aorta, arch and descending aorta, with plaques shown in panels B and C.

Three dimensional reconstruction of image A—anterior view of the ascending aorta.

Three dimensional reconstruction of image A—left anterior oblique view of aortic arch and descending aorta.