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Increased aortic intima-media thickness following Kawasaki disease

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ABSTRACT

Background and aims: The cardiovascular risk following Kawasaki disease (KD), especially in those without coronary artery changes or with regressed coronary artery lesions, is unclear. We assessed markers of early atherosclerosis in individuals following KD, including those with and without coronary artery abnormalities.

Methods: We performed a cross-sectional case-control study of 60 patients (25 with always normal coronary arteries and 35 with abnormalities) and 60 controls, at least two years after KD. Non-invasive assessment of arterial structure (carotid and aortic intima-media thickness (IMT)) and function (pulse wave velocity, carotid artery distensibility and diameter compliance) was done. Analyses were adjusted for traditional cardiovascular risk factors.

Results: Kawasaki disease patients had increased aortic IMT compared to controls (0.53 mm (95% CI 0.51–0.56) *versus* 0.49 (95% CI 0.47–0.52), $p = 0.04$), largely driven by those with abnormal coronary arteries. There were no differences in carotid IMT. Kawasaki disease patients with coronary artery abnormalities had reduced carotid distensibility compared to controls (15.16% (95% CI 13.67–16.65) *versus* 17.50 (95% CI 16.43–18.58), $p = 0.02$).

Conclusions: Patients with KD have increased aortic IMT and reduced carotid distensibility, indicating heightened cardiovascular risk, especially in those with coronary artery abnormalities. In our study, we used validated surrogates for cardiovascular disease risk. Our findings, therefore, warrant follow-up investigations in KD patients.

1. Introduction

Kawasaki disease (KD), an acute systemic vasculitis of unknown etiology, is the leading cause of acquired heart disease in children living in industrialized countries [1,2]. The majority of children treated with intravenous immunoglobulin do not develop coronary artery aneurysms [3], but the possibility of more generalized increased cardiovascular risk following KD remains an unresolved and key issue in long-term management of this patients' population [4].

Increased coronary artery intima-media thickness (IMT) and abnormal vasodilatory responses have been described at sites of regressed coronary artery aneurysms and in normal coronary artery segments [5,6]. Atherosclerotic changes with thrombus formation are reported in coronary artery aneurysms of young adults post KD [7–9], as has acute myocardial infarction in young adults following uncomplicated KD [10].

Non-invasive assessment of the structure and function of extra-coronary vasculature, extrapolated from studies of subclinical atherosclerosis, has been used to investigate cardiovascular risk post KD. Findings are inconsistent and abnormalities have been reported both in patients with 'always normal' coronary arteries and in those with coronary artery abnormalities, particularly in Asian populations [11]. Frequently used assessment methods include carotid IMT, pulse wave velocity (PWV), and endothelial function of peripheral arteries, although the latter is less well tolerated in children [11,12].

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In non-KD studies, aortic IMT is a widely used non-invasive measure in infants and children [13–17]. Early pre-atherosclerotic lesions develop in the aorta of fetuses, infants, and children [18–20]. Measurement of the aortic IMT using ultrasound is feasible, reproducible using a standardized research protocol, and well-tolerated in the pediatric population [14,15,21]. It has been suggested to be an earlier and more discriminatory measure of early atherosclerosis than carotid IMT in high risk children, including those with hypercholesterolemia, diabetes [16], and inflammatory bowel disease [13]. Furthermore, evidence of inflammatory, structural and functional changes in the aorta has been reported in a mouse model [22] and in a human KD study using ultrasound [23]. Aortic IMT has not previously been investigated following KD.

We aimed to investigate cardiovascular risk following KD using a comprehensive range of methods assessing both arterial structure (carotid and aortic IMT) and function (PWV, carotid artery distensibility and diameter compliance) in a cross-sectional case-control study. Our hypothesis was that, compared to controls of similar age and sex, KD patients have increased carotid and aortic IMT, faster PWV, and reduced carotid artery distensibility and diameter compliance, indicative of heightened cardiovascular risk.

2. Patients and methods

Patients aged 6–30 years, who had KD at least two years previously, were recruited from The Royal Children's Hospital and Monash Medical Centre, Melbourne, Australia. Individuals with a history of acute KD that fulfilled either the American Heart Association diagnostic criteria for KD (Supplementary Table 1) [24], and/or had abnormal coronary artery dimensions that met the Japanese Ministry of Health Criteria [25] on an echocardiogram performed within two months of disease onset, were included in the KD group. The first echocardiogram was done as an inpatient following the diagnosis of KD, with a second one performed approximately six weeks later if no abnormality was found initially. Closer surveillance was tailored according to the presence and severity of coronary artery aneurysm(s) found. Kawasaki disease patients were further categorised into those with 'always normal' coronary arteries (nCA) and those with abnormal coronary arteries (abnCA) based on their maximum coronary artery diameter measured on the echocardiogram. The Human Research Ethics Committee of both hospitals approved the study and written informed consent was obtained from the parents or adult patients. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki.

Control participants were unrelated healthy individuals of similar age and sex to the KD patients recruited from The Royal Children's Hospital Melbourne, children of staff members, or unrelated friends of the KD patients. Exclusion criteria in both groups were pregnancy, diabetes, known atherosclerotic cardiovascular disease, treatment for hypertension and/or hyperlipidemia, or chronic inflammatory conditions. Assessments were deferred for at least 4 weeks following an acute febrile illness.

Participants attended the Murdoch Childrens Research Institute on a single occasion after a minimum 6-h fast between September 2013 and December 2015 during which, demographic details and anthropometric measurements (BC 418, Tanita, Tokyo, Japan) were obtained. Blood pressure (SphygmoCor® XCEL, AtCor Medical Pty Ltd, NSW, Australia) was measured in the right arm in the supine position after at least 5 min of rest. The mean of three measurements was recorded. High sensitivity C-reactive protein (hsCRP, Abbott Architect, IL, USA), glucose, triglycerides, total cholesterol, HDL and LDL cholesterol (Vitros 5600, Ortho-Clinical Diagnostics, NJ, USA) were measured in blood obtained at the study visit. Pubertal stage was assessed based on self-report using the Tanner scale.

2.1. Intima-media thickness and pulse wave velocity

Ultrasound images of the carotid artery and the abdominal aorta were acquired with Vivid i (General Electronics Healthcare, U.S.A) using a linear probe with a frequency of at least eight MHz, with simultaneous ECG gating as described previously [26]. Images of the right carotid artery were optimized to visualize the intima-media complex of the anterior and posterior walls of the common carotid artery one cm proximal to the carotid bulb. Cine loops of at least five cardiac cycles were recorded for offline analysis.

The abdominal aorta was identified in the lower abdomen and followed distally until the aortic bifurcation was visualized. Details of the scanning and procedure were described previously [14]. Briefly, images of the distal 10–15 mm of aorta focused on the far wall were optimized and two to five cine loops recorded. Simultaneous ECG grating was used and all IMT measurements were performed on the R wave of the ECG.

The intima-media thickness (the distance from the lumen-intima interface to the media-adventitia interface) of the far wall, one cm from the carotid bulb, was measured at end-diastole (R-wave on ECG) using a semi-automated analysis software, Carotid Analyzer for Research (Medical imaging applications LLC, Iowa, USA). Once the media-adventitia borders were validated by the operator, the lumen-intima boundaries were automicatally detected by the software and adjusted by the operator as necessary. The 'mean IMT' is the average intima-media thickness in the selected area of measurment while the 'maximum IMT' is the largest intima-media measurement within that segment. The mean of these 'mean IMT' or 'maximum IMT' measurements from three to five end-diastolic frames was calculated and used in the analyses. The minimum carotid lumen diameter, diameter distensibility ((maximum diameter-minimum diameter)/(minimum diameter) x 100%), and diameter compliance ((maximum diameter-minimum diameter)/pulse pressure) were calculated by the Carotid Analyzer software once the borders were set. The peripheral pulse pressure was used to calculate the diameter compliance instead of the central pulse pressure because the transfer function for estimating central aortic pressure waveform from radial tonometry pressure has not been validated in children [27].

The five best quality frames of the abdominal aorta were selected from the recorded cine loops for analysis using the same procedure. Due to the poor image quality of the proximal aortic wall, lumen diameter, diameter distensibility and diameter compliance were not measured. All the carotid and aortic IMT were measured by a trained single grader (KC) blinded to the subject status. Intra-rater reproducibility for replicate mean carotid IMT and aortic IMT was assessesed in a random sample of 10 participants. The mean absolute difference and SD was 0.01 ± 0.03 mm for carotid IMT and 0.01 ± 0.07 mm for aortic IMT between the two repeated measurements.

Arterial stiffness is assessed by carotid femoral PWV by SphygmoCor® XCEL (AtCor Medical Pty Ltd, NSW, Australia) using a standardized protocol. In summary, the distance between the arterial measurement sites was measured and this value was divided by the transit time between the two sites based on the foot-to-foot arterial waveform measurements to derive the PWV. The pulse wave was captured using a tonometer over the carotid artery and a thigh cuff that detected the femoral pulse. Only results meeting the in-built quality control criteria were analyzed. The mean of three measurements from each participant was recorded.