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Kawasaki Disease and Cardiovascular Risk: A Comprehensive Review of Subclinical Vascular Changes in the Longer Term

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ABSTRACT

Studies of subclinical vascular changes post Kawasaki disease indicate that, in general, individuals with a history of coronary artery aneurysms have increased carotid intima-media thickness, evidence of endothelial dysfunction, and increased arterial stiffness, possibly indicative of heightened cardiovascular risk. The results are less consistent for low risk groups.

Conclusion: Until data are available from larger prospective studies, it is prudent to advise families of individuals with a history of Kawasaki disease to minimise traditional modifiable cardiovascular risk factors.

Key words: carotid intima-media thickness, endothelial function**,** Kawasaki disease, mucocutaneous lymph node syndrome, vascular stiffness

Key Notes:

- Whether Kawasaki disease increases later cardiovascular risk, especially in low risk patients, is an increasingly important clinical issue.
- Although not entirely consistent across studies, individuals with a history of coronary artery aneurysms have increased carotid intima-media thickness, evidence of endothelial dysfunction, and increased arterial stiffness, while results are less consistent for low risk groups.
- Individuals with a history of Kawasaki disease should minimise traditional modifiable cardiovascular risk factors.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic pediatric vasculitis of unknown etiology. KD may damage the coronary arteries, resulting in a spectrum of injury including coronary artery aneurysms in the most severe cases. The incidence is increasing and it is the commonest cause of paediatric acquired heart disease in industrialized countries.(1) First described in 1967,(2) those who had the disease in the 1960s and 1970s are now entering middle-age. Whether KD increases later cardiovascular risk, especially in those with no identified coronary artery changes or with regressed changes, is therefore an increasingly important clinical issue.

Non-invasive assessment of arterial structure and function, extrapolated from studies of subclinical atherosclerosis has been used to estimate future cardiovascular risk in those with previous KD. These methods include carotid artery intima-media thickness (cIMT),(3) pulse wave velocity (PWV),(4) and endothelial function of peripheral arteries,(5) which are predictive of incident cardiovascular outcomes related to atherosclerosis in adults, but whose predictive value in children is less clear. Here, we review studies on these subclinical vascular changes following KD, with a particular focus on KD patients without coronary artery changes, or whose changes have regressed. We highlight limitations in evaluating KD-related cardiovascular risk using these methods. Biomarkers of endothelial injury or vascular health are beyond the scope of this review.

METHODS

Searches of the databases MEDLINE and PUBMED were completed in October 2015. The Medical Subject Headings (MeSH) term *mucocutaneous lymph node syndrome* and key word *Kawasaki disease* were combined with MeSH terms and key words for each assessment method: (1) MeSH terms: *atherosclerosis, vascular stiffness, carotid intima-media thickness* (2) key words: *carotid intima-media thickness, endothelial function, flow-mediated dilatation, peripheral arterial tonometry, arterial stiffness, pulse wave velocity*. Original studies published in English with healthy controls and KD patients in the convalescent phase were included. Reference lists from retrieved articles were examined for other relevant studies. Some authors were contacted to clarify queries regarding their studies.

RESULTS

The most widely studied vascular assessment method in KD is cIMT (16 studies of 881 KD cases). There are 13 studies on flow-mediated dilatation (FMD), nine on PWV, and three on peripheral arterial tonometry (PAT) (Table 1). Most studies are small, cross-sectional, and vary considerably in methodology and the time elapsed since KD. For these reasons, a meta-analysis was not performed. Furthermore, most studies combine participants with regressed or persistent aneurysms in analyses. When results are available for each group individually, this is highlighted in the tables.

Table 1: Methods for studying subclinical vascular changes in KD and their association with cardiovascular risk

Carotid intima-media thickness (cIMT)

Measurement of the cIMT using B-mode ultrasound is a non-invasive, sensitive, and reproducible method to identify asymptomatic individuals at increased risk of cardiovascular events.(3) Traditional cardiovascular risk factors in childhood are predictive of cIMT thickness and progression in young adults.(6) Data on cIMT following KD consist largely of cross-sectional studies with small sample sizes, varying ethnicity, age of participants, and time since illness, differences in methodology, and differences in definition of coronary artery aneurysm (Table 2). The oldest patient was 42 years old and the longest time elapsed since the acute illness was 35 years.(7) Most studies do not adjust for vessel size, an important consideration in differentiating a physiologically thicker cIMT in a larger artery from pathological changes.(8)

Table 2 Studies of carotid intima-media thickness (cIMT) in individuals who had Kawasaki disease in childhood

Coronary artery aneurysms and Asian ethnicity are the factors most strongly associated with increased cIMT. Studies which consist exclusively of patients with either persistent or regressed coronary aneurysms,(7, 9, 10) or with predominantly more severe KD patients,(11) report significantly increased cIMT. Even in studies with participants of predominant European descent, cIMT tends to be greater in groups with persistent coronary aneurysms. (18, 22)

Studies predominantly involving those of Asian ethnicity (including Japanese) report increased cIMT despite small sample sizes.(7, 9-12) Notably, three Japanese studies did not detect significant differences in cIMT.(13, 16, 17) In one, possible differences may have been confounded by an older

and smaller group of controls.(13) In the other, coronary artery aneurysm is defined by z-scores rather than the Japanese ministry of health criteria of absolute coronary artery diameter more commonly used in Japanese studies. (16) The z-score is a more sensitive measure of coronary artery size than the Japanese ministry of health criteria.(24) However minor changes in the absolute diameter measurement may lead to major changes in z-score, so that the group with coronary aneurysms may have had less severe coronary artery changes compared to studies using Japanese ministry of health criteria.

In contrast, in the largest study to date in which participants are predominantly of European ancestry, no differences in cIMT were found in participants with always normal or mildly ectatic coronary arteries.(18) Similarly, no structural differences were found in all KD patients in a recent large UK study. (20) On the other hand, a recent Dutch study noted increased cIMT in participants with a history of KD regardless of presence of aneurysms in the subacute phase.(19) Only two studies focus exclusively on KD patients without coronary artery changes or with transient coronary artery dilatations; both have small sample sizes and neither detected any differences in cIMT compared to controls.(21, 23) Overall, irrespective of ethnicity, studies performed on average less than 10 years since acute KD are more likely to detect increased cIMT compared to controls, although data are inconsistent.(9, 11, 12, 19, 22) When the difference in cIMT between cases and controls is plotted against age, the difference diminishes over time in those with always normal coronary artery, but the difference persists in those with a history of coronary artery aneurysm.(19) This suggests that changes in cIMT may be reversible (e.g. arising from inflammation) and subsides over time in the low risk group.

The clinical significance of increased cIMT in some KD patients is unknown. Despite statistically significant differences, the increase in cIMT in KD patients relative to controls is in general less than 0.2 mm. A 0.2 mm or greater increase in cIMT in adult prospective studies is associated with an increased risk of cardiovascular event in adults.(25) There are no prospective studies investigating changes in cIMT over time in KD patients, nor its association with subsequent cardiovascular events.

Endothelial function

Flow-mediated dilatation (FMD)

Endothelial dysfunction is one of the earliest changes in atherosclerosis. Endothelial injury, which can be induced by inflammation, results in reduction in endothelium-derived relaxing factors and consequently reduced vasodilatation under standardized conditions.(26) FMD measures the

percentage increase in the size of the brachial artery using ultrasound before and after suprasystolic occlusion, and is predictive of cardiovascular events in adults.(5)

Ten out of 13 studies in KD show a decrease in FMD compared to controls, regardless of ethnicity, time since acute illness, and presence of coronary artery aneurysms, suggesting that endothelial dysfunction may follow KD in some patients (Table 3). Several studies report an incremental decrease in FMD in patients with persistent coronary aneurysms,(13, 15, 16, 27, 28) and importantly, also in low-risk patients.(15, 16, 27-30) Significant changes in FMD are found in KD patients with no detectable differences in cIMT.(13, 15, 16) This is consistent with studies in atherosclerosis in which functional arterial changes precede structural abnormalities.(31)

Table 3 Studies of flow-mediated dilatation (FMD) in individuals who had Kawasaki disease in childhood

Three studies show no changes in FMD; 2 studies have less than 15 KD patients each.(23, 35) McCrindle *et. al* found no difference in FMD in predominantly European patients with persistent coronary aneurysms despite metabolic and lipid abnormalities.(34) It is unknown if there are consistent ethnic differences in endothelial function following KD.

Peripheral arterial tonometry (PAT)

PAT is another non-invasive measure of endothelial function. In contrast to FMD, it measures microvascular endothelial function in the digital arteries by finger plethysmograph, which detects pulse volume changes before and after suprasystolic brachial artery occlusion.(36) A smaller PAT index is associated with cardiovascular risk factors.(36) PAT and FMD data may not be directly comparable, as they measure parameters in the microcirculation and large arteries respectively, and there are no paediatric data comparing the two methods. All studies in Table 4 are performed using Endo-PAT 2000 (Itamar Medical, Caesarea, Israel). The data from the three studies using PAT in KD are more variable than those using FMD. The oldest patient was 41 years of age and the longest time elapsed after the acute illness was 34 years.(37) One study detected significant differences,(38) whereas two others did not.(18, 37) As with all measures of endothelial function, environmental (ambient temperature, time of the day) and participant (food and alcohol intake, speaking, sleeping, position and white coat effect) factors may affect results.(39)

Table 4 Studies of peripheral arterial tonometry (PAT) in individuals who had Kawasaki disease in childhood

Pulse wave velocity (PWV)

Measurement of arterial PWV is a noninvasive and reproducible method for determination of arterial stiffness.(40) Various methods are used to determine regional, local and systemic arterial stiffness. Carotid-femoral PWV, which measures central aortic stiffness either by Doppler or applanation tonometry, is generally accepted as the gold standard.(41) In adults, an increased aortic PWV predicts cardiovascular events above and beyond traditional risk factors.(4) Brachial-ankle PWV is technically easier as only blood pressure cuffs are required, however, results are affected by assessment of multiple vascular segments contemporaneously and it may be a sub-optimal measure of central arterial stiffness. Measurements of PWV are also influenced by environmental and participant factors.(41)

Studies of PWV in KD are cross-sectional and single-centered, similar to the other intermediate vascular phenotypes studies (Table 5). The oldest patient studied was 35 years of age and the longest time elapsed since acute KD was 28 years.(28) Different methodologies are used, as described. Despite these limitations, the majority of studies show an increased in PWV following KD regardless of patient ethnicity, time since acute illness, and presence of coronary artery aneurysms. An incremental increase in PWV in those with persistent coronary aneurysms is also reported.(11, 42) One study found a significant increase in PWV but did not detect changes in cIMT.(14) Of note, a recent large study from the UK did not detect any differences in PWV in all KD patients of varying severity.(20)

Table 5 Studies of pulse wave velocity (PWV) in individuals who had Kawasaki disease in childhood

DISCUSSION

Kawasaki disease and atherosclerosis – two distinct routes to the same destination?

Whether KD results in accelerated atherosclerosis *per se*, or whether vascular changes following KD and atherosclerosis represent distinct but partially overlapping pathogenic processes, albeit with potentially similar clinical outcomes that result from coronary artery stenosis and thrombus formation, is unclear. Early atherosclerotic lesions result from infiltration of lipid laden macrophages (foam cells) and other inflammatory cells into the arterial wall with proliferation of smooth muscle cells.(47) Chronic inflammation of the arterial wall is common to atherosclerosis and KD, but other features differ. In contrast to atherosclerosis, lipid deposition in the arterial intima is

unusual in KD. Characteristic features of acute coronary arteritis in KD are oedema, leukocyte infiltration, and myointimal proliferation.(48) Transmural inflammation and disruption of the basement membrane and elastic lamina contribute to aneurysm formation in KD and intimal fibrosis is notable during arterial remodeling.(48)

However, there is evidence of atherosclerosis following KD; atherosclerotic changes with thrombus formation in aneurysmal regions of coronary arteries are reported in young adults with previous KD.(48-50) Acute myocardial infarction is reported in young adults post low risk KD who did not have traditional atherosclerotic risk factors.(51) Reports of lipid profile post KD are conflicting.(18, 20, 21, 42, 52) A recent study utilizing nuclear magnetic resonance for lipoprotein particle concentration analysis (which better differentiate atherogenic subgroups of lipoproteins) did not show a worse lipid profile in individuals with a history of KD.(53) It is plausible that KD may promote atherosclerosis following an acute inflammatory vascular injury, in keeping with the 'response-to-injury' hypothesis, suggested to underlie atherosclerosis development more broadly.(31) Furthermore, biomarkers indicative of endothelial injury has been reported years after acute KD, even in those with echocardiographically normal coronary arteries, suggesting that persistent vascular damage may continue.(20) In general, however, the typical coronary artery histopathology post-KD appears distinct from that of atherosclerosis.

Coronary artery aneurysms

The most important complication in KD is coronary artery aneurysm formation, which may rarely result in myocardial infarction and sudden death. In the current era, most children with KD are treated with high dose intravenous immunoglobulin (IVIG) and therefore have morphologically normal coronary arteries on echocardiography.(52) To date, favorable outcomes have been reported in these low-risk patients. In a north American cohort 15 years after acute KD, the overall risk of cardiovascular events in patients is the same as controls, with events only occurring in patients with persistent coronary artery aneurysms.(54) In a 15-year follow-up study of Japanese patients, no stenosis is detected following small or medium size coronary artery aneurysms and eventually 90% of aneurysms regressed.(55)

However, there is accumulating evidence of abnormal coronary vascular structure and function independent of clinical echocardiographic detection of coronary aneurysms. With the use of intravascular ultrasound, thickened intima-media complex is found at sites of regressed coronary artery aneurysms and angiographically normal segments.(56) Coronary arteries with regressed aneurysms demonstrate abnormal vasodilatation responses to isosorbide dinitrate and nitroglycerin.(57) There are no published longitudinal data relating these coronary vascular structure

and functional changes in regressed coronary aneurysms with subsequent adverse cardiovascular outcomes. These differences in coronary arteries post-KD may indicate a heightened cardiovascular risk and highlight the potential insensitivity of echocardiography in detecting persistent vascular abnormalities.

Limitations of echocardiography in long term risk-stratification

Echocardiography remains the primary imaging modality to support the identification of coronary artery abnormalities and allow risk-stratification in acute KD. It is non-invasive and has high sensitivity and specificity for detecting proximal coronary artery aneurysms.(58). When compared to cardiac magnetic resonance imaging, echocardiography lacks sensitivity both for detecting coronary aneurysms, particularly distal ones, and luminal changes.(59) Furthermore, there may be a spectrum of coronary artery involvement so that a dichotomous classification (coronary artery aneurysm either present or absent based on echocardiography alone), often used in follow-up studies, may be insensitive. In a retrospective study, patients whose coronary artery z scores remain < 2.5 but have z scores that increase during the course of their KD illness by > 2 on serial measurements have higher levels of inflammatory markers and trend towards immunoglobulin resistance, compared to those patients whose coronary artery z scores are < 2.5 but did not increase by > 2 on serial measurements.(60) It is unclear whether the long-term risk of cardiovascular disease is increased in the majority of children with apparently 'low risk' KD as defined by echocardiographic assessment of the coronary arteries; subclinical vascular changes may complement echocardiographic findings in furthering our understanding of the longer term risk.

What can we conclude from available data on subclinical vascular changes post-Kawasaki disease?

Studies of subclinical vascular changes highlight the spectrum of vascular abnormalities that may be associated with KD. Overall, those with coronary artery aneurysms have evidence of persistent vascular structural changes (increased cIMT), endothelial dysfunction (decreased FMD), and increased arterial stiffness (increased PWV) compared to controls, although data are inconsistent. It is uncertain whether the subclinical vascular changes of those with regressed aneurysms differ from those with persistent aneurysms as no studies to date are of adequate size to explore this question definitively. KD patients with no history of coronary artery aneurysms, in general, have similar cIMT compared to controls, but some data indicate endothelial dysfunction and increased arterial stiffness. The long-term clinical implications of these subclinical vascular differences are unclear; this is particularly important as the assessment tools were developed for studies of atherosclerosis rather than KD.

CONCLUSION

Despite the emerging data in this area, there is still uncertainty whether low-risk KD patients are at increased risk of cardiovascular disease. A spectrum of functional and structural changes suggest that understanding cardiovascular risk in KD patients should be more nuanced than simple stratification by coronary artery dimensions. Prospective longitudinal studies, ideally using methods specific for detecting KD related changes to study the association of subclinical vascular differences with long term cardiovascular outcomes, are warranted. Until data are available on the longer-term risk and outcomes, it is prudent to advise families to maintain a healthy lifestyle following KD and to minimize traditional modifiable cardiovascular risk factors such as smoking, hyperlipidemia, hypertension, hyperglycemia, and obesity.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

LIST OF ABBREVIATIONS USED

Kawasaki disease (KD)

Carotid artery intima-media thickness (cIMT)

Pulse wave velocity (PWV)

Flow-mediated dilatation (FMD)

Peripheral arterial tonometry (PAT)

Coronary artery aneurysm (CA)

Not available (N/A)

Standard deviation (SD)

Interquartile range (IQR)

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Table 1: Methods for studying subclinical vascular changes in KD and their association with cardiovascular risk

	Abbreviations	Type of vascular structure or function measured	Association with increased cardiovascular risk
Carotid intima-media thickness	cIMT	Intima-media complex of the carotid artery	Increased carotid intima-media thickness
Flow-mediated dilatation	FMD	Endothelial function	Smaller percentage increase in the diameter of the brachial artery following cuff release after suprasystolic occlusion
Peripheral arterial tonometry	PAT	Endothelial function	Smaller pulse volume increase in the digital arteries following cuff release after suprasystolic brachial artery occlusion
Pulse wave velocity	PWV	Arterial stiffness	Increased pulse wave velocity

Table 2 Studies of carotid intima-media thickness (cIMT) in individuals who had Kawasaki disease in childhood

Study	References	No. of cases	Age (SD) in years	Time (SD or range) since diagnosis	Ethnicity	Type of cIMT measurement	Carotid intima-media thickness (SD) in mm						
							Control	Always normal coronary arteries	P value	Persistent or regressed coronary artery aneurysm(s)	P value	Giant aneurysm(s)	P value
Noto *et al* 2009	(7)	35	20.5 (9.3)	18.6 (8.4) y	Japanese	Maximum	0.46 (0.05)	N/A	N/A	↑ 0.57 (0.15)	<0.001*	N/A	N/A
Noto *et al* 2001	(9)	20	16.6 (4.1)	9.8 (4) y	Japanese	Maximum	0.48 (0.08)	N/A	N/A	↑ 0.54 (0.09)	<0.05*	N/A	N/A
Noto *et al* 2012	(10)	18	17.2 (5.3)	14.1 (6.9) y	Japanese	Maximum	0.42 (0.04)	↑0.54 (0.08)			<0.001*	N/A	N/A
Cheung *et al* 2007	(11)	50	8.6 (2.8) CA 8.6 (3.3) no CA	7.4 (3.5) y CA 5.8 (2.1) y no CA	Chinese	Mean	0.36 (0.04)	↑ 0.39 (0.04)	0.008*	↑ 0.41(0.04)	<0.001*	N/A	N/A
Meena *et al* 2013	(12)	27	8.2 (2.6)	2.4 (16-73) m	Indian	Maximum *(average of measurements 3 months apart)*	0.42 (0.07)	↑0.50 (0.08)		↑0.49 (0.07)	<0.001#	N/A	N/A

Ikemoto *et al* 2005	(13)	65	13 (9-22)	12 (5-21) y	Japanese	Mean	0.5 (0.04)	↔ 0.47 (0.06)	N/A	↔ 0.49 (0.05) *<4mm CA* ↔ 0.4 (0.05) *4-8mm CA*	N/A	↔0.52 (0.05) *>8mm*	N/A

Table 2 Studies of carotid intima-media thickness (cIMT) in individuals who had Kawasaki disease in childhood (continued)

Study	**References**	**No. of cases**	**Age (SD or range) in years**	**Time (SD or range) since diagnosis**	**Ethnicity**	**Type of cIMT measurement**	**Carotid intima-media thickness (SD) in mm**						
							Control	**Always normal coronary arteries**	**P value**	**Persistent or regressed coronary artery aneurysm(s)**	**P value**	**Giant aneurysm(s)**	**P value**
Lee *et al* 2009	(14)	25	12.6 (2.0)	>8 y	Korean	Mean	0.50 (0.01)	↔0.41 (0.19)			N/A	N/A	N/A
Kadono *et al* 2005	(15)	24	8.3 (4.1)	5.8 (4.6) y	Japanese	Maximum	0.46 (0.06)	↔0.45 (0.07)			N/A	N/A	N/A

Ishikawa *et al* 2013	(16)	24	6.5 (1.7)	3.3 (2.2-5.7) y	Japanese	Mean	0.43 (0.04)	↔ 0.43 (0.02)		↔ 0.45 (0.03)	0.90[#]	N/A	N/A
Oguri *et al* 2014	(17)	75	8.2 (2.8)	2.3 (2.8) y	Japanese	Mean	0.39 (0.04)	↔0.40 (0.03)			0.15[*]	N/A	N/A
Selamet Tierney *et al* 2013	(18)	203	16.73 (4.21)	11.6 (1.2-26) y	Predominantly Caucasian	Mean-Left	0.43 (0.03)	↔ 0.44 (0.04)		↔ 0.43 (0.03)		↑0.47 (0.05) *>8mm*	0.05[#]
						Mean-Right	0.43 (0.03)	↔ 0.43 (0.02)		↔ 0.43 (0.03)		↔0.42 (0.02)	0.41[#]

Table 2 Studies of carotid intima-media thickness (cIMT) in individuals who had Kawasaki disease in childhood (continued)

Study	**References**	**No. of cases**	**Age (SD) in years**	**Time (SD or range) since diagnosis**	**Ethnicity**	**Type of cIMT measurement**	**Carotid intima-media thickness (SD or range) in mm**						
							Control	**Always normal coronary arteries**	**P value**	**Persistent or regressed coronary artery aneurysm(s)**	**P value**	**Giant aneurysm(s)**	**P value**
Dietz *et al*	(19)	161	12.0 (3.3)	8.0 (6.1-10.9) y	Predominantly	Mean (*average of*	0.36 (0.003)	↑ 0.38 (0.002)	<0.001	↑ 0.37 (0.006)	0.06	0.41 (0.010)	<0.01

2015					Caucasian	*bilateral internal, common, and carotid bulbs)*							
Shah *et al* 2015	(20)	92	11.9 (4.3-32.2)	8.3 (1.0-30.7) y	Predominantly Caucasian	Mean-Left	0.46 (0.40-0.60)	↔0.47 (0.37-0.53)	0.99	↔0.46 (0.39-0.58)	0.95		
						Mean-Right	0.47 (0.40-0.60)	↔0.47 (0.39-0.58)	0.59	↔0.47 (0.39-0.57)	0.92		
Gupta-Malhotra *et al* 2009	(21)	28	20.9 (6)	16 (6) y	Mixed	Not reported *(average of bilateral)*	0.48 (0.06)	↔ 0.5 (0.01)	>0.20*	↔0.47 (0.01) *Transient CA*	N/A	N/A	N/A
Dalla Pozza *et al* 2007	(22)	20	12.1 (4.7)	4.1 (3.6) y	German	Mean	0.42 (0.01)	↑ 0.44 (0.02)		↑ 0.46(0.02)	<0.05#	N/A	N/A
Laurito *et al* 2013	(23)	14	10 (3.7)	6.3 (4.8) y	Italian	Mean *(average of bilateral)*	0.50 (0.10)	↔ 0.50 (0.10)			0.93*	N/A	N/A

↑ = increased compared to controls, ↓ = decreased compared to controls, ↔ = No change compared to controls, m = months, y = years, CA= Coronary artery aneurysms, N/A= Not Available, * = P value when comparing one specific KD group with controls, # = P value of the trend comparing KD groups with controls

Table 3 Studies of flow-mediated dilatation (FMD) in individuals who had Kawasaki disease in childhood

Table 3 Studies of flow-mediated dilatation (FMD) in individuals who had Kawasaki disease in childhood (continued)

Study	References	No. of cases	Age (SD or range)	Time (SD or range) since diagnosis	Change (SD, range or IQR) in size of brachial artery in the hyperemic phase (%)				
					Control	Always normal coronary arteries	P values	Persistent or regressed coronary artery aneurysm(s)	P value
Noto *et al* 2009	(7)	35	20.5 (9.3) y	18.6 (8.4) y	13.3 (SD 4.8)	N/A	N/A	↓9.1 (SD 2.7)	<0.001*
Ishikawa *et al* 2013	(16)	24	6.5 (1.7) y	3.3 (2.2-5.7) y	11.1 (range 10.1-13.9)	↓ 9.1 (IQR 6.6-10.7)	<0.05*	↓ 4.4 (IQR 2.6-5.7)	<0.01*
Kadono *et al* 2005	(15)	24	8.3 (4.1) y	5.8 (4.6) y	11.7 (SD 14.7)	↓ 8.3 (SD 9.1)		↓ -0.5 (SD 9.2)	<0.05#
Dhillon *et al* 1996	(29)	20	13 (11-19) y	11.3 (5.3-17.1) y	9.4 (range 5-15)	↓ 3.1(range 0-10) *All normal or regressed CA*			<0.001*
Niboshi *et al* 2008	(28)	35	27 (4.2) y	24.1 (4.5) y	14.4 (SD 3.2)	↓ 11.5 (SD 2.8)		↓ 8.8 (SD 2.2) *Persistent CA* ↓ 9.6 (SD 2.1) *Regressed CA*	<0.05#
Ghelani *et al* 2009	(30)	20	8.4 (2.3) y	25.3 (20) m	12.23 (SD 8.93)	↓ 5.7 (SD 9.19)	0.02*	N/A	N/A

↑ = increased compared to controls, ↓ = decreased compared to controls, ↔ = no change compared to controls, m = months, y = years, CA= coronary artery aneurysms, SD =

Study	References	No. of cases	Age (SD or range)	Time (SD or range) since diagnosis	Change (SD, range or IQR) in size of brachial artery in the hyperemic phase (%)				
					Control	Always normal coronary arteries	P values	Persistent or regressed coronary artery aneurysm(s)	P value
Deng *et al* 2003	(32)	39	7.1 (2.7) y	3.4 (2.1) y	14.1 (SD 6.8)	↓ 6.2 (SD 3.9)			<0.001*
Ikemoto *et al* 2005	(13)	65	13 (9-22) y	12 (5-21) y	18.8 (SD 2.8)	↔ 19.4 (SD 3.9)		↓8.9 (SD 2.8) *4-8mm CA* ↓ 4.2 (SD 1.5) *>8 mm CA*	<0.001#
Liu *et al 2009*	(27)	41	7 (3-11)	5 (1.6-10)y	12.1 (SD2.3)	↓9.5 (SD2.8)	<0.01*	↓4.5 (SD 1.5) *Persistent CA*	<0.01*
Huang *et al 2008*	(33)	11	12.9 (2.5) y	10.7 (3.0) y	13.1 (SD1.0)	N/A		↓6.1 (SD 1.6) *Persistent CA*	<0.001*
McCrindle *et al* 2007	(34)	52	15.5 (2.3) y	11.2 (3.7) y	10 (IQR 2-15)	↔10 (IQR 2-18)		↔5 (IQR 0-10) *Regressed CA* ↔10 (IQR 2- 20) *Persistent CA*	0.59#
Laurito *et al* 2013	(23)	14	10 (3.7) y	6.3 (4.8) y	9.5 (SD 1.8)	↔9.38 (SD 1.4)			0.79*
Borzutzky *et al* 2008	(35)	11	10.6 (2) y	8.1 (3.6) y	8.0 (SD 2.9)	↔11.1 (SD 5.7)			0.12*

standard deviation, IQR interquartile range, N/A= Not Available, * = P value when comparing one specific KD group with controls, # = P value of the trend comparing KD groups with controls

Table 4 Studies of peripheral arterial tonometry (PAT) in individuals who had Kawasaki disease in childhood

Study	References	No. of cases	Age (SD) in years	Time (SD or range) since diagnosis in years	Peripheral arterial tonometry index- ratio of pulse amplitude in hyperemia compared to baseline (SD)				
					Control	Always normal coronary arteries	P value	Persistent or regressed coronary artery aneurysm(s)	P value
Tobayama *et al* 2013	(37)	14	31.5 (5.5)	28.6 (5.6)	1.89 (0.51)	↔ 2.03 (0.44)			0.19*
Pinto *et al* 2013	(38)	19	21 (6)	>5	2.31 (0.53)	↓ 1.67 (0.49)	<0.001*	N/A	
Selamet Tierney *et al* 2013	(18)	203	16.73 (4.21)	11.6 (1.2-26)	1.70 (0.53)	↔ 1.79 (0.44)		↔ 1.72 (0.53) *z>3* ↔ 1.62 (0.35) *>8mm CA*	0.55#

↑ = increased compared to controls, ↓ = decreased compared to controls, ↔ = no change compared to controls, CA= coronary artery aneurysms, N/A= Not Available, * = P value when comparing one specific KD group with controls, # = P value of the trend comparing KD groups with controls

Table 5 Studies of pulse wave velocity (PWV) in individuals who had Kawasaki disease in childhood

Study	References	Method	No. of cases	Age (SD or range) in years	Time (SD or range) since diagnosis in years	Pulse wave velocity(SD) in cm/sec				
						Control	Always normal coronary arteries	P value	Persistent or regressed coronary artery aneurysm(s)	P value
Lee *et al* 2009	(14)	Brachial ankle	25	12.6 (2.0)	>8	984.0 (96.5)	↑ 1020.6 (146.5)			<0.05*
Ooyanagi *et al* 2004	(43)	Brachial ankle	90	13 (5)	11 (6)	688 (104)	↔ 691 (119)	N/A	↔ 739 (128)	N/A
Niboshi *et al* 2008	(28)	Brachial ankle	35	27 (4.2)	24.1 (4.5)	Male 1161 (114) Female 1040 (140)	↑ Male 1248 (136) ↔ Female 1061 (92)			<0.05*
Cheung *et al* 2007	(11)	Brachial-radial	50	8.6 (2.8) *CA* 8.6 (3.3) *no CA*	7.4 (3.5) *CA* 5.8 (2.1) *no CA*	577 (1.25)	↑ 673 (1.88)	0.01*	↑ 722 (1.67)	0.009*
Nakagawa *et al* 2015	(44)	Brachial ankle	201	10 (4)	7.0 (3.9)	913 (121)	↑ 886 (135)	0.04*	N/A	N/A
Cho *et al* 2014	(42)	Brachial-radial	68	8.0 (1.89) *CA* 7.22 (1.49) *no CA*	5.7 (2.6) *CA* 4.4 (2.2) *no CA*	966.71 (88.70)	↑ 1076.86 (164.10)		↑ 1181.50 (7.78)	<0.001#
Alhuzaimi *et al*	(45)	Aortic	42	9.4 (4.3)	6.1 (3.8)	370 (61)	↑ 495 (286)			0.006*

2013		(Doppler)								
Vaujois *et al* 2013	(46)	Aortic (Doppler)	89	10.6 (5.9)	6.8 (5)	494.26 (218.24)	↑ 573.38 (224.10)	0.005*	↔ 561.51 (208.54)	0.11*
Shah *et al* 2015	(20)	Carotid-radial	92	11.9 (4.3-32.2)	8.3 (1.0-30.7) y	730 (470-960)	↔750 (460-1120)	0.25	↔740 (490-1120)	0.86
		Carotid-femoral				540 (400-840)	↔570 (390-900)	0.58	↔510 (380-700)	0.13

↑ = increased compared to controls, ↓ = decreased compared to controls, ↔ = no change compared to controls, CA = Coronary artery aneurysms, N/A= Not Available, * = P value when comparing one specific KD group with controls, # = P value of the trend comparing KD groups with controls