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# Vascular health late after Kawasaki disease: implications for accelerated atherosclerosis

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Kawasaki disease (KD), an acute vasculitis that primarily affects young children, is the most common acquired paediatric cardiovascular disease in developed countries. While sequelae of arterial inflammation in the acute phase of KD are well documented, its late effects on vascular health are increasingly unveiled. Late vascular dysfunction is characterized by structural alterations and functional impairment in term of arterial stiffening and endothelial dysfunction and shown to involve both coronary and systemic arteries. Further evidence suggests that continuous low grade inflammation and ongoing active remodeling of coronary arterial lesions occur late after acute illness and may play a role in structural and functional alterations of the arteries. Potential importance of genetic modulation on vascular health late after KD is implicated by associations between mannose binding lectin and inflammatory gene polymorphisms with severity of peripheral arterial stiffening and carotid intima-media thickening. The changes in cholesterol and lipoproteins levels late after KD further appear similar to those proposed to be atherogenic. While data on adverse vascular health are less controversial in patients with persistent or regressed coronary arterial aneurysms, data appear conflicting in individuals with no coronary arterial involvements or only transient coronary ectasia. Notwithstanding, concerns have been raised with regard to predisposition of KD in childhood to accelerated atherosclerosis in adulthood. Until further evidence-based data are available, however, it remains important to assess and monitor cardiovascular risk factors and to promote cardiovascular health in children with a history of KD in the long term.

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## Introduction

Kawasaki disease (KD) is the most common acquired cardiovascular disease in children in developed countries<sup>1)</sup>. This acute vasculitis, which affects primarily infants and young children, can have multiorgan involvements<sup>2)</sup>. While systemic involvement is generally self-limiting, cardiovascular complications can be life-threatening<sup>3)</sup>. Acute inflammatory damage to coronary and systemic arteries in the early phase of the illness has been well described<sup>4)</sup>. A recent animal study using a KD mouse model suggested an important pathophysiologic link between coronary arteritis and subsequent acceleration of atherosclerosis, implicating that KD in childhood may potentially predispose to early atherosclerosis in adulthood<sup>5)</sup>. Studies in adults with acute coronary syndrome also provided evidence of persistent risk of thrombosis in regressed coronary aneurysms<sup>6)</sup>. Indeed, long-term structural alteration and functional disturbance of coronary and systemic arteries are increasingly recognized in adolescents and young adults with a history of KD. The focus of this review is on vascular health and cardiovascular risk profile late after KD, which may have implications on accelerated atherosclerosis in adulthood.

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## Late coronary arterial abnormalities

### 1. Structural alteration

Structural alteration of coronary arterial wall after KD has been demonstrated using intravascular ultrasound. Sugimura et al.<sup>7)</sup> reported in KD patients examined at about 9 years after the acute illness intimal thickening and calcification at sites of the coronary aneurysms, and thickened but smooth intima at sites of regressed coronary aneurysms. Importantly, intimal thickening has been noted even in angiographically normal coronary arterial segments near to the site of persistent or regressed aneurysm. Similarly, Suzuki et al.<sup>8)</sup> have described thickened intima-media complex at sites of persistent and regressed aneurysms and in angiographically normal coronary arterial segments. Using virtual histologic-intravascular ultrasound, Mitani et al.<sup>9)</sup> found heterogeneous plaque areas with varying composition of fibrosis, fibrofatty, necrotic core, and dense calcium areas and provided insights into the potential role of atherogenesis in the evolution of coronary arterial lesions late after KD. In a pathological study of patients with history of KD who died after 15 years of age<sup>10)</sup>, new intima thickening that superimposes on pre-existing intima thickening has been observed in coronary arteries with no previous formation of aneurysms.

While regression of coronary aneurysms is well described in KD<sup>3)</sup>, new or expanding aneurysms have also been reported late after the acute illness<sup>11-14)</sup>. The timing of detection of new aneurysms after KD ranges from 2 to 19 years after the acute phase<sup>14)</sup>. The development of new aneurysms has been hypothesized to be related to abnormal arterial structures with superimposed haemodynamic disturbance in the presence of stenotic lesions. While clinical events associated with expanding aneurysms appear uncommon<sup>14)</sup>, expanding aneurysms may be at risk of rupture<sup>11)</sup> and thrombosis.

Quantification of coronary arterial calcification has been used to assess the risk of developing coronary heart disease in asymptomatic adults with atherosclerosis<sup>15)</sup>. During long-term follow-up of patients with KD, coronary arterial calcifications have been detected using electron beam computed tomography<sup>16-18)</sup>. In a prospective, cohort study of 18 patients with KD at >1 year from the acute disease onset, coronary calcification was found in four of five patients with late echocardiographic abnormalities, but not in the 13 patients with no or resolved coronary arterial involvement<sup>17)</sup>. Sudden death occurred in one patient who had the highest calcium score. The role of electron beam computed tomography-detected coronary arterial calcifications in the risk stratification of patients with KD warrants further assessments.

### 2. Coronary arterial stiffening

Endothelium-independent coronary dilation in patients with

KD has been assessed by intracoronary infusion of agents that directly relax arterial smooth muscle. Sugimura et al.<sup>19)</sup> and Iemura et al.<sup>20)</sup> reported impairment of coronary vasodilatory response to intracoronary injection of isosorbide dinitrate at sites of persistent and regressed aneurysms. Similarly, impaired coronary vasoreactivity to intracoronary nitroglycerin at sites of regressed aneurysms has been shown<sup>8)</sup>. In the latter study, decreased nitroglycerin reactivity has also been observed in segments without evidence of aneurysmal dilation. These data suggest that stiffening of the coronary artery occurs after KD, which may be related to smooth muscle dysfunction and pathological changes secondary to coronary arteritis.

### 3. Coronary endothelial dysfunction

In normal coronary arteries, local infusion of acetylcholine induces the release of nitric oxide from an intact endothelium to cause vasodilation and forms the basis of endothelial functional assessment<sup>21)</sup>. On the other hand, paradoxical constriction of atherosclerotic coronary arteries may result from direct muscarinic action of acetylcholine on vascular smooth muscle. In patients with KD studied late after the acute illness, acetylcholine-induced constriction of coronary arteries with persistent and regressed aneurysms has been found<sup>20,22,23)</sup>.

Cold pressor test performed in conjunction with positron emission tomography can also be used to assess coronary endothelial function. In coronary arteries with normally functioning endothelium,  $\beta$ -adrenergic activation due to cold stress increases coronary flow and induces vasodilation secondary to shear stress-induced release of nitric oxide from endothelial cells. On the other hand, the significantly lower myocardial blood flow found in patients with regressed aneurysms late after KD suggests coronary endothelial dysfunction<sup>24)</sup>.

Although the exact mechanism of coronary endothelial dysfunction years after the acute illness remains to be elucidated, ongoing active vascular remodeling and chronic inflammatory processes as discussed below may be possible explanations. Existing data suggest endothelial dysfunction at sites of persistent and regressed aneurysms, but it remains controversial whether angiographically normal coronary arteries are similarly involved<sup>22,23)</sup>.

### 4. Reduced myocardial flow reserve

Myocardial flow reserve as assessed by positron emission tomography<sup>24)</sup> and induction of hyperaemia by dipyridamole<sup>25)</sup> or adenosine triphosphate<sup>26)</sup> has been examined in patients with KD. In patients with regressed coronary aneurysms<sup>26)</sup> and even in those without documented coronary arterial lesions<sup>24,25)</sup>, myocardial flow reserve has been shown to be reduced. The global rather than regional blood flow abnormalities suggest diffuse reduction of dilation capacity of the microcirculation.

Indeed, these findings agree with the diffuse nature of the vasculitic process as demonstrated by pathological<sup>27)</sup> and intravascular ultrasonography<sup>8)</sup> examinations. Although the clinical implications of these findings during childhood are unclear, reduced myocardial flow reserve is undoubtedly of significance in the event of superimposed coronary artery disease during adulthood. Using three-dimensional speckle tracking echocardiography, Yu et al.<sup>28)</sup> recently showed impairment of left ventricular strain in patients with and even in those without coronary aneurysms after the acute illness.

## Late systemic arterial abnormalities

### 1. Increased carotid intima-media thickness

Carotid intima-media thickness has been regarded as a surrogate marker of atherosclerosis in adults<sup>29)</sup>. In children with coronary aneurysms complicating KD, Noto et al.<sup>30)</sup> reported carotid intima-media thickening. Some small scale and nonage matched studies<sup>31,32)</sup>, however, reported no differences in carotid intima-media thickness between patients and controls and among patients with varying involvement of coronary arteries. Subsequent studies that included age-matched controls or age-adjusted standard deviation scores of intima-media thickness revealed carotid intima-media thickening not only in patients with coronary aneurysms, but also in those without coronary artery lesions<sup>33,34)</sup>. A recent study of North American children and young adults, however, showed normal vascular health indices including carotid intima-media thickness in KD patients whose maximum coronary arterial dimensions had always been normal or only mildly ectatic<sup>35)</sup>. However, the mean left carotid intima media thickness tended to differ across different KD subgroups, being highest in patients with giant coronary arterial aneurysms. Whether the conflicting data are related to differences in ethnic backgrounds of study cohorts require further clarifications.

There have been discussions on whether thickening of the intima-media complex represents early atherosclerosis changes or a distinct KD vasculopathy related to luminal myofibroblastic proliferation<sup>36)</sup>. The recent finding of a higher grey scale median of the carotid intima-media complex in patients with KD suggests that sclerotic vascular remodeling after KD may be distinct from the atherosclerotic remodeling, which has a lower grey scale median often observed in familial hypercholesterolaemia<sup>37)</sup>.

### 2. Systemic arterial endothelial dysfunction

High-resolution ultrasound assessment of reactive hyperaemia of the brachial artery in response to sphygmomanometer cuff occlusion has been used to assess systemic arterial endothelial function based similarly on the principle of endothelium-de-

pendent release of nitric oxide in response to shear stress<sup>38)</sup>. Using this technique, Dhillon et al.<sup>39)</sup> demonstrated significant reduction of brachial arterial flow-mediated dilation in KD patients, even in those without detectable coronary artery involvement, at a median of 11 years after the acute disease. In adults with a history of KD, flow-mediated dilation has similarly been found to be impaired<sup>40)</sup>. Other investigators have, however, reported endothelial dysfunction only in patients with persistent coronary artery lesions<sup>31)</sup>, being worse in those with coronary arterial aneurysms<sup>32)</sup>. Others have, on the other hand, reported on normal brachial arterial flow-mediated dilation in patients with KD<sup>41,42)</sup>. The conflicting data in the literature and their possible reconciliation is discussed later in this review. Nonetheless, given the pathological processes during acute illness of endothelial necrosis and leukocyte infiltration of medium-sized arteries<sup>43,44)</sup>, the late functional abnormalities of the brachial artery endothelium may be a long-term consequence of diffuse systematic inflammation.

### 3. Systemic arterial stiffening

Increased cross-sectional stiffness of carotid artery has been found in patients with KD with and without coronary aneurysms late after the acute illness<sup>30,33,45)</sup>. The magnitude of carotid arterial stiffening was further shown to be related to serum high-sensitivity C-reactive protein concentrations<sup>45)</sup> and carotid intima-media thickness<sup>33)</sup> but not alternations in lipid profile<sup>30)</sup>. Increased regional stiffness of the aorta and brachioradial and brachial-ankle arterial segments, as evidenced by increased pulse wave velocity, has further been shown in patients with KD<sup>46-49)</sup>.

Arterial stiffness is directly related to characteristic impedance of the arterial bed, the pulsatile component of the afterload presented to the left ventricle. Indeed, invasive studies have shown significantly increased characteristic impedance and reduced total peripheral arterial compliance in patients with KD<sup>50)</sup>, suggesting that both central and peripheral arterial wall stiffness is increased after KD. Importantly, this abnormal profile was found regardless of persistence of coronary arterial lesions. Structural alteration and endothelial dysfunction probably contribute to stiffening of the arterial tree in patients with KD late after the acute illness. Reparative process in the convalescent and chronic phase of the illness is characterized by intimal thickening, fibrous scar formation, and smooth muscle proliferation<sup>51-55)</sup>, which may lead to an increase in vascular wall stiffness. Endothelial dysfunction may act by increasing vasomotor tone<sup>56,57)</sup>. Stiffening of the arterial wall may increase intraluminal stress due to an increase in pulse pressure<sup>58)</sup> and predispose to vascular damage and atherosclerosis. The possibility of establishing a feedback loop in patients with KD has been hypothesized<sup>33)</sup>. Indeed, carotid intima media thickness in KD patients has been shown to correlate with carotid arterial stiffness, after adjustment for potential confounding influence of age, sex, systemic blood pressure, and

serum cholesterol levels<sup>33</sup>.

#### 4. Genotype and arterial sequelae

An association between mannose binding lectin gene mutation and coronary arterial complications has been reported in infants with KD<sup>59</sup>. Studies have furthermore shown modulating effects of mannose binding lectin genotypes on peripheral conduit arterial stiffness late after KD<sup>60</sup>. Patients with intermediate- or low-level mannose binding lectin expression genotypes were found to have stiffer peripheral conduit arteries than those with high-level expression genotypes. The mechanism of the modulating effects of mannose binding lectin genotypes remains speculative. Given that mannose binding protein binds to mannose and N-acetyl glucosamine residues on the surface of many microbial antigens and plays a role in complement activation and opsonization of microorganisms, a low serum mannose binding lectin level may be associated with delayed clearance of the triggering infectious agent, hence resulting in more significant acute arterial inflammation and late dysfunction. Indeed, inflammatory gene polymorphisms have been shown to influence vascular health of patients with KD late after the acute illness<sup>61</sup>. Specifically, *C-reactive protein* +1444 C>T and *tumour necrosis factor- $\alpha$* -308 G>A polymorphisms are shown to be associated with increased carotid arterial stiffness and intima media thickness in the long-term.

### Chronic low-grade inflammation

While widespread inflammatory damage of the coronary and other medium-sized muscular arteries occurs during the acute phase of KD, there is increasing evidence that vasculitis may continue in a low-grade fashion in the long-term<sup>62-64</sup>. In fatal cases of KD with despite apparent resolution of vascular inflammation and the absence of early detectable coronary artery abnormalities, the histological findings of infiltration of lymphocytes and plasma cells in the arterial wall suggest smoldering vasculitis<sup>62,63</sup>. Persistence of low-grade chronic inflammation is further evidenced by increased serum high-sensitivity-C-reactive protein concentrations in children and adolescents with a history of KD complicated by coronary aneurysm formation, whether persistent or regressed<sup>45,65</sup>. The recent demonstration of persistent inflammation *in vivo* in a 40-year-old man with giant coronary aneurysm by positron emission tomography supports the concept of continuous smoldering vasculitis<sup>66</sup>.

Inflammatory processes play a pivotal role in atherogenesis<sup>67</sup>. The inflammatory response to vascular injury involves recruitment and activation of monocytes through activation of monocyte chemoattractant protein-1<sup>67</sup>, which exerts its action by

interacting with the chemokine receptor CCR2 on the surface of monocytes<sup>68</sup>. Cheung et al.<sup>69</sup> demonstrated significant induction of monocyte chemoattractant protein-1 and CCR2 expression in THP-1 macrophages *in vitro* by the serum of children with a history of KD. C-reactive protein has been shown to upregulate CCR-2 expression in human monocytes<sup>70</sup>. Persistent elevation of baseline CRP level after KD<sup>45,65</sup> may therefore play a role in chronic stimulation of the MCP-1/CCR2 pathway. Indeed, the magnitude of gene induction was found to correlate with serum high sensitivity-C-reactive protein level<sup>69</sup>. *In vitro* studies have further confirmed increased expression of monocyte chemoattractant protein-1 in coronary aneurysmal tissue from patients undergoing coronary artery bypass grafting<sup>70,71</sup>. Taken together, these findings suggest that chronic low-grade inflammation is associated with and may perhaps predispose to long-term structural and functional changes of arteries in patients with KD.

There is further evidence of ongoing active remodeling of coronary artery lesions even late after KD. In patients who died at 2 to 12 years after onset of KD, extensive expression of vascular growth factors including transforming growth factor  $\beta_1$ , platelet-derived growth factor A, and basic fibroblast growth factor was found within and surrounding smooth muscle cells at stenotic and recanalized sites<sup>72</sup>. Limited histological evidence suggests a similar increase in the expression of vascular growth factors even in clinically normal coronary arteries after KD<sup>73</sup>.

### Dyslipidaemia

Lipid abnormalities, specifically decreased total cholesterol, high-density lipoprotein (HDL)-cholesterol, and apoA-I levels, have been found in the acute phase of KD<sup>74-77</sup>. Newburger et al.<sup>74</sup> further reported persistently reduced HDL cholesterol levels even at 3 years after the initial illness. Cheung et al.<sup>46</sup> further showed that at a mean of 7.1 years after the acute illness, patients with KD and coronary aneurysms had lower HDL cholesterol and apolipoprotein A-I levels and higher apolipoprotein B levels, while in patients without aneurysms, the apolipoprotein B levels are also higher than controls. As severity of vasculitis in the acute phase may be reflected by development of coronary complications<sup>78</sup>, the findings of this latter study suggest that the magnitude of acute inflammation may have important relationships with late lipid abnormalities.

The alterations in cholesterol and lipoprotein profiles late after KD are similar to those predisposed to atherogenesis. Endothelial dysfunction documented late after resolution of the acute illness<sup>39</sup> may diminish lipoprotein lipase activity with reduced generation of HDL cholesterol<sup>74</sup>. Furthermore, inhibition of lipoprotein lipase may decrease apoA-I level by increasing its catabolism<sup>79</sup>. In adults with chronic inflammation due to rheumatoid arthritis,

increased LDL cholesterol levels have been reported<sup>80)</sup>. Given the evidence of low-grade chronic inflammation late after the acute illness, changes in lipid profile may be a reflection of such process.

## Controversies

Notwithstanding the identification of vascular risk factors late after KD, evidence to the contrary exists in the literature. A number of explanations to reconcile conflicting data, especially in individuals of no coronary arterial involvements, has been proposed<sup>81)</sup>. The relatively small sample size of different studies, the variable means to assess arterial stiffness and endothelial function, coexistence of other cardiovascular risk factors, and possible ethnic differences may have accounted for the different findings and conclusions.

While alteration of arterial structure and function in patients with persistent or regressed coronary artery aneurysms is less controversial, the major question of whether vascular health late after the acute illness in individuals with no or only transient coronary arterial involvement will be similar to that of healthy subjects remains unanswered. The cardiovascular outcomes of the early Japanese cohorts who reach middle and older age would hopefully shed light on the answers to this issue<sup>82)</sup>. In the latest update based on follow-up until 2009, for patients with cardiac sequelae due to KD, the mortality rate was significantly higher than that of the general population. On the other hand, the mortality rates of both male and female patients who did not have cardiac sequelae did not show any increase. Nonetheless, only about 6% of the entire cohort has reached age 30 to date.

## Conclusions

Structural alteration and functional disturbance of coronary and systemic arteries, chronic low grade inflammation, and dyslipidaemia may exist in children and young adults with a history of KD late after the acute illness, in particular in those with persistent or even regressed coronary aneurysms. Notwithstanding the existence of conflicting data, concerns have been raised with regard to predisposition of KD in childhood to accelerated atherosclerosis in adulthood. Until further evidence-based data are available, it remains important to assess and monitor cardiovascular risk factors and to promote cardiovascular health in children with a history of KD in the long term.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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