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## Chapter

# Cardiovascular Health in Kawasaki Disease

*Mitsuru Seki*

## Abstract

Kawasaki disease (KD) is a self-limiting vasculitis of unknown etiology primarily affecting young children. The most important aspect in the treatment of KD is the prevention of coronary artery lesions (CALs) because myocardial ischemia or infarction due to coronary artery stenosis or occlusion may be lethal. In addition, patients with a history of KD have systemic vasculitis, which indicates vascular endothelial damage. Therefore, patients with CAL are at a high risk of atherosclerosis. While some reports have shown an increase in vascular stiffness, others have not, and the presence of atherosclerotic lesions in patients with KD is controversial. Appropriate acute-phase treatment to prevent CAL and systemic vasculitis and subsequent regular follow-ups are important. This chapter deals with the cardiovascular health of patients with a history of KD.

**Keywords:** vasculitis, aortic stiffness, atherosclerosis, vascular health

## 1. Introduction

Kawasaki disease (KD) was first reported as acute febrile mucocutaneous lymph node syndrome by Tomisaku Kawasaki in 1967. KD is a self-limited vasculitis affecting children mainly under 5 years of age, the etiology is still unknown [1, 2]. KD is one of the most common acquired cardiac disorders in children, causing coronary artery dilatation or aneurysms. Coronary artery lesion (CAL) develop in approximately 25% of KD patients who do not receive appropriate treatment [3]. As KD is a systemic vasculitis, vessel walls other than coronary arteries are affected. KD patients with cardiovascular complications should be closely monitored for cardiovascular events throughout their lives. Furthermore, even in the absence of obvious complications, patients with a history of KD are likely to experience underlying vascular endothelial damage. This chapter deals with long-term cardiovascular health in this population.

## 2. Epidemiology

KD is a systemic vasculitis that mainly affects children younger than 5 years of age. Currently, more than 60 countries in Asia, the Middle East, the Americas, Africa, and Europe have reported KD cases [4]. The incidence of KD is high in Japan, Korea, and Taiwan, but low in North America and European countries. These incidences

reported in different regions of the world can be affected by the survey/surveillance methods used, clinical diagnostic and treatment practices, physician awareness of KD, and data sources used to estimate incidence [5].

According to a nationwide epidemiological survey of KD in Japan, more than 15,000 patients were reported annually until 2019, which was before Coronavirus disease 2019 (COVID-19) pandemic [6]. The annual number of patients with KD in Japan was 17,364 in 2019; however, it decreased to 11,173 in 2020. The incidence rate (per 100,000 children aged 0–4 years per year) was 370.8 (410.1 in boys, and 329.4 in girls) in 2019, and 238.8 (267.3 in boys, and 208.9 in girls) in 2020. Although infectious factors or foreign antigens can trigger KD, the cause of this syndrome remains unclear. Several children diagnosed with COVID-19 have developed multisystem inflammatory syndrome in children (MIS-C), which shows KD-like symptoms [7, 8]. On the other hand, the decline in the incidence of KD remains small, despite the extreme reduction in common pediatric infectious diseases during the COVID-19 pandemic period in Japan, KD may be triggered by unidentified respiratory pathogens that can be acquired both within and outside the household [9].

Genetic factors appear to be involved in KD pathogenesis, as suggested by the highest incidence among Asians and Pacific Islanders, and in boys versus girls. In a genome-wide linkage study, several functional polymorphisms such as *inositol 1,4,5-trisphosphate 3-kinase C (ITPKC)* and *caspase-3 (CASP3)* have been identified as common susceptibility genes for KD. Siblings of children with KD have an increased risk of developing the disease [10]. Sibling pairs with KD within a short time interval may be due to environmental triggers, including infectious antigens. Both genetic and environmental factors are thought to interact with each other during the onset of KD; therefore, a detailed study of these contributing factors may help elucidate the pathogenesis of KD.

### 3. Histopathology of vasculitis

The histopathological characteristics of KD are as follows: (1) major muscular arteries branching from the aorta, including the coronary arteries, are predominantly injured; (2) the damaged arteries are extra-arterial, not arteries within organs; (3) acute vasculitis occurs synchronously throughout the body; and (4) vasculitis is a proliferative inflammation consisting of an abnormal accumulation of monocytes/macrophages.

KD is characterized by inflammation of the coronary artery in the acute phase, which usually lasts for approximately 6 weeks. The earliest histological changes in coronary arteritis are seen on sixth to eighth day of illness, starting with the infiltration of inflammatory cells in the tunica adventitia and tunica intima. Inflammatory cells infiltrate the tunica media, leading to inflammation of all layers of the vessel wall by the tenth day of illness. Subsequently, the artery begins to dilate owing to significant damage to the internal elastic lamina or tunica media. Inflammatory cell infiltration continues for approximately 2 weeks and then gradually fades. If the vessel wall undergoes a certain degree of damage, even after vasculitis subsides, inflammatory scarring of the coronary artery remains for a long time. In particular, in patients with coronary aneurysms, various findings, such as stenotic lesions or extensive calcification of the aneurysm wall, are observed [11].

In addition to the coronary arteries, other systemic blood vessels are injured by vasculitis [12]. Whole-body examination for KD to evaluate systemic vasculitis shows

vascular damage at various sites, especially in the subclavian, brachial, axillary, and iliac arteries. Many case reports have revealed that systemic arterial aneurysms are almost always associated with giant coronary arterial aneurysms, and a detailed evaluation should be considered in these patients.

#### 4. Diagnosis and acute therapy for KD

The recent diagnostic guidelines in Japan are shown in **Table 1** [13]. The typical clinical symptoms are shown in **Figure 1**. Acute treatment should be initiated immediately after diagnosis to prevent cardiovascular complications. Although the incidence of CAL was reported in 23–43% of patients treated only with aspirin, treatment with IVIG and aspirin for four consecutive days reduced the incidence of CAL to 8–15% [14, 15]. Moreover, a single infusion of 2 g/kg IVIG, which is the current standard regimen, reduces the incidence of CAL to 4.6% [16]. Therefore, IVIG is currently the standard therapy for acute KD. A systematic review by the Cochrane Collaboration revealed that the development of CAL can be reduced by a single dose of 2 g/kg IVIG administered before the tenth day of illness [17].

The risk of developing CAL is closely related to responsiveness to treatment. KD patients with IVIG resistance are at an increased risk of developing CALs compared

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Principal clinical features
<ol style="list-style-type: none"><li>1. Fever.</li><li>2. Bilateral bulbar conjunctival injection.</li><li>3. Changes of lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa.</li><li>4. Rash (including redness at the site of Bacille Calmette- Guerin (BCG) inoculation).</li><li>5. Changes of peripheral extremities: (Initial stage) reddening of palms and soles, edema. (Convalescent stage) periungual desquamation.</li><li>6. Non-supparative cervical lymphadenopathy.</li></ol>
Other significant demographic, clinical, echocardiographic, and laboratory features
<ol style="list-style-type: none"><li>1. Kawasaki disease may be suspected in the presence of fewer than four principal clinical features when the following findings are observed:<ul style="list-style-type: none"><li>• Elevation of hepatic transaminases early in the course of the disease.</li><li>• Increased leukocytes in the urine sediment of an infant.</li><li>• Thrombocytosis in the convalescent phase</li><li>• Elevation of BNP or NT-pro BNP</li><li>• Mitral valve regurgitation or pericardial effusion by echocardiography</li><li>• Enlargement of the gallbladder (hydrops of gallbladder)</li><li>• Hypoalbuminemia or hyponatremia</li></ul></li><li>2. If a KD patient manifests the following findings, the patient should be considered for admission of a critical care unit.<ul style="list-style-type: none"><li>• Hemodynamically significant myocarditis</li><li>• Hypotension (shock)</li><li>• Paralytic ileus</li><li>• Decreased level of consciousness</li></ul></li></ol>

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3. Risk scores to predict intravenous immunoglobulin resistance may be applied to guide patient management. The following features are elements of the risk scores for predicting intravenous immunoglobulin resistance.
- Leukocytosis with left shift
  - thrombocytopenia
  - hypoalbuminemia
  - hyponatremia
  - hyperbilirubinemia (jaundice)
  - elevation of CRP
  - Age <1 year
- 
4. Other non-specific findings which may be observed in Kawasaki Disease and should not exclude the diagnosis.
- Irritability
  - Cardiovascular: abnormal extra heart sounds, electrocardiogram changes, aneurysm of peripheral arteries other than coronary (axillary etc.),
  - Gastrointestinal: abdominal pain, vomiting, diarrhea
  - Hematologic: increased erythrocyte sedimentation rate, anemia
  - Dermatologic: micropustular rash, transverse grooves across the finger nails.
  - Respiratory: cough, rhinorrhea, retropharyngeal edema, infiltrate on chest radiograph.
  - Rheumatologic: pain, swelling.
  - Neurologic: cerebrospinal fluid pleocytosis, seizures, facial nerve palsy, paralysis of the extremities.
- 

**Table 1.**  
*Diagnostic guideline for Kawasaki disease.*



**Figure 1.**  
*Typical clinical symptoms of Kawasaki disease. (a) Bulbar conjunctival injection, (b) Reddening of lips, (c) Redness at the site of Bacille Calmette-Guerin inoculation.*

to IVIG responders; therefore, various additional treatments such as prednisolone, infliximab, cyclosporine, urinary trypsin inhibitors, and plasma exchange have been established to prevent CAL.

In addition, to improve the prognosis of CALs, several risk-scoring systems to predict IVIG non-responders before initial treatment have been established and are widely used in clinical practice in Japan [18–20]. For patients with a high-risk score, two randomized control trials revealed the efficacy of a first-line combined treatment strategy, IVIG and prednisolone or IVIG and cyclosporin A [21, 22]. As several reports from other countries revealed that these risk-scoring systems are inadaptable to the prediction of IVIG non-responders in regions other than Japan [23, 24], it may be desirable to develop risk-scoring systems that can be used globally or an original scoring system to be adapted to each region for the suppression of KD vasculitis. Although these strategies have improved the prognosis of coronary arteries, the occurrence of giant coronary aneurysms is still observed, and further treatment is desirable.

## 5. Cardiovascular risk and management

KD is a systemic vasculitis that can lead to atherosclerosis due to vascular dysfunction and damage. Long-term management should consider the cardiovascular risk of atherosclerosis progression in both coronary arteries and systemic vessels.

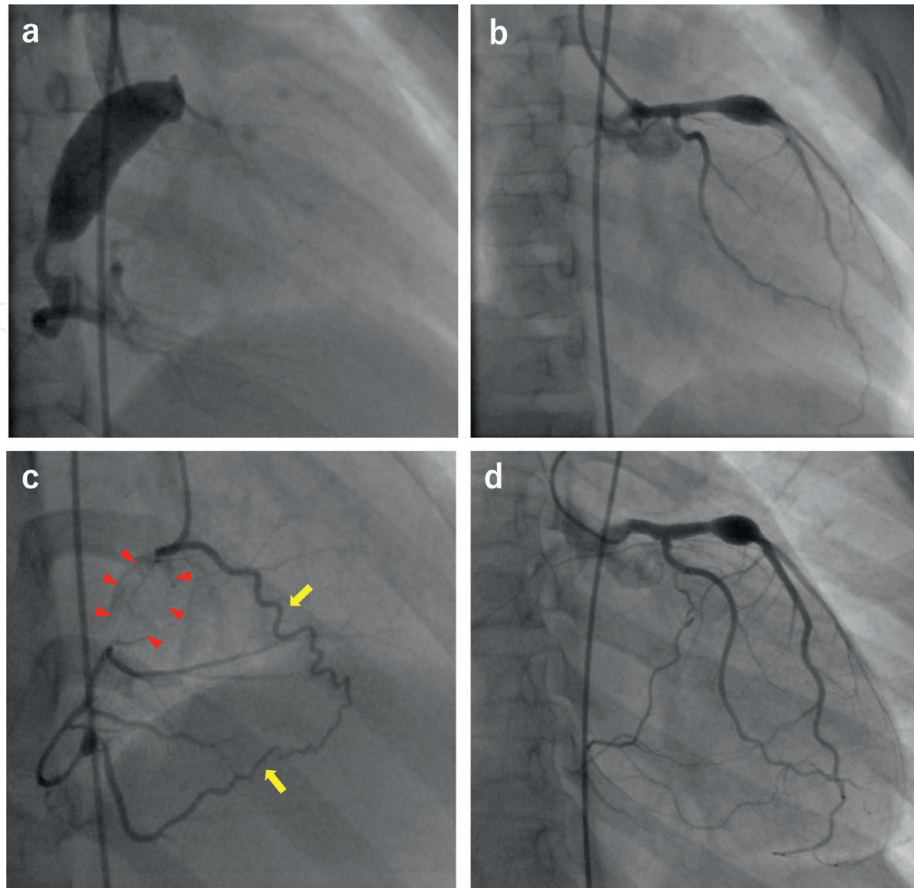
### 5.1 Coronary arteries

Coronary artery aneurysms that remain 30 days after the onset of KD are defined as cardiovascular complications of KD. Aneurysms impair vascular endothelial function and thrombus formation. **Figure 2** shows the giant aneurysms identified angiographically in patients with IVIG-resistant KD. This can lead to angina or myocardial infarction owing to coronary artery stenosis or occlusion. In addition, calcification of the vessel wall is frequently observed. However, it is estimated that 75% of coronary aneurysms regress within 3 years of onset [25]. Even when aneurysms remain, they often become smaller in diameter than those in the early stages.

The management strategies in the follow-up stage included (1) prevention of thrombosis in aneurysms and myocardial infarction, (2) early diagnosis of myocardial ischemia and appropriate reperfusion therapy, and (3) management of the risk of atherosclerosis and preventive education.

#### 5.1.1 Prevention of thrombosis in aneurysms and myocardial infarction

In KD patients with CAL, it is important to prevent cardiac events. In general, these patients require aspirin or other antiplatelet agents. Anticoagulants are administered mainly in cases of giant coronary artery aneurysms. Additionally, statin therapy may improve chronic vascular inflammation and endothelial dysfunction, which has been suggested to be useful for vascular health. Statins have multifaceted pharmacological effects, including anti-inflammatory, antioxidant, anticoagulant, and thrombolytic effects, as well as a decrease in serum cholesterol levels. Additionally, statins are expected to be effective in improving vascular endothelial function. According to a statement from the American Heart Association, KD patients with CAL need to be treated prophylactically.



**Figure 2.** Giant aneurysms. (a), (b) Coronary angiography in 4-year-old patient with giant aneurysms. This patient was treated with warfarin and aspirin since diagnosis of giant aneurysm. (a) Selective right coronary arteriography. Giant aneurysm was identified. (b) Selective left coronary arteriography. Medium size aneurysm was identified at left anterior descending artery. (c), (d) Follow-up coronary angiography at age 9 (5 years later). (c) Selective right coronary arteriography. Giant aneurysm was occluded (red arrow head) and collateral arteries had developed to the periphery of the right coronary artery (yellow arrow). (d) Selective left coronary arteriography. Medium size aneurysm did not change significantly and no stenotic lesions were detected.

### 5.1.2 Early diagnosis of myocardial ischemia and appropriate reperfusion therapy

Critical stenotic lesions are sometimes observed at the proximal and distal ends of coronary aneurysms. These findings are believed to be caused by vascular remodeling. Coronary artery stenosis was evaluated using coronary angiography, coronary functional flow reserve, enhanced coronary computed tomography, and stress myocardial scintigraphy. These tests should be performed periodically depending on the severity of the coronary artery aneurysm. Although coronary revascularization is required in less than 1% of patients with a history of KD, percutaneous coronary intervention or coronary artery bypass grafting is required when myocardial ischemia is detected using these modalities.

### 5.1.3 Management of risk of atherosclerosis and the preventive education

In cases of aneurysms larger than medium size, vascular endothelial dysfunction, chronic inflammation in the vessel wall, and subsequent vascular remodeling continue to occur even late after the onset of KD. Although the details have not yet been elucidated, vascular endothelial damage and chronic inflammation resemble the early lesions of atherosclerosis and may be predisposing factors for future atherosclerosis.

Therefore, it is necessary to actively eliminate cardiovascular risk factors at a younger age. In other words, education on the prevention of hypertension and obesity, smoking cessation, management of blood sugar and lipids, and reduction of psychological stress are important for long-term management.

## 5.2 Systemic vessels

It is well known that vascular stiffness increases in the atherosclerotic vasculature. Patients with KD have systemic vasculitis because inflammation occurs in medium-sized muscular arteries throughout the body. While some KD patients show vessel lesions throughout the body, the association between KD vasculitis in the acute phase and atherosclerosis in long-term follow-up remains unclear.

The relationship between atherosclerotic lesions and the development of myocardial infarction has long been established in adult patients. It has also been reported that increased aortic stiffness is associated with coronary atherosclerosis, as such, this could be an important predictive marker for cardiovascular events [26]. Given these findings, KD patients with CAL may be at risk of developing atherosclerosis.

It is well known that functional impairment of vascular endothelial cells exists before morphological changes such as vascular intima-media thickening. Recently, the importance of assessment of vascular function has been suggested for vascular health. Although several evaluation methods have been reported, these parameters have mainly been published to understand the pathophysiology of vascular dysfunction in KD. In the future, these indices should be implemented in clinical practice and used for the appropriate follow-up of patients with KD. The following is an overview of each indicator:

### 5.2.1 Percentage change in flow-mediated dilatation: %FMD

Percentage change in flow-mediated dilatation (%FMD) reflects endothelial nitric oxide-dependent vasodilatation. A significant decrease in %FMD is a common feature of atherosclerosis in adults. Some meta-analyses reported that %FMD was lower in the KD group than in the control group, indicating endothelial damage and a risk of atherosclerosis [27–29]. Several previous studies have reported that the %FMD was significantly lower in patients with a history of KD than in control subjects, showing systemic endothelial dysfunction late after KD onset [30–32]. Interestingly, in pediatric patients with CAL late after KD, there is increased high-sensitivity C-reactive protein in addition to reduced %FMD, indicating the presence of ongoing chronic vascular inflammation and endothelial dysfunction [31].

### 5.2.2 Pulse wave velocity: PWV

Noninvasive evaluations of vascular elasticity have also been well documented. Pulse-wave velocity (PWV) is a representative parameter for evaluating arterial stiffness. PWV is a simple and noninvasive test for evaluating arterial stiffness. PWV can be measured from various arterial sites, and pressure waveforms are usually obtained percutaneously at the common carotid and femoral arteries. Several methods have been developed to measure PWV, including aortic PWV, brachial-radial PWV, and brachial-ankle PWV. There have been some reports on the measurement of brachial-radial or brachial-ankle PWV, showing a significant increase in arterial stiffness in the KD group compared with the control group, regardless of whether the patients had



CAL [33–35], however, the relationship between vascular stiffness and prognosis is not clear. Although aortic PWV is a known predictor of cardiovascular events [36], no large prognostic studies examining the association between brachial-radial or brachial-ankle PWV and cardiovascular events have been performed. This limitation should be noted when the PWV is used.

### 5.2.3 Cardio-ankle vascular index: CAVI

The cardio-ankle vascular index (CAVI) is a representative parameter for evaluating arterial stiffness. Because CAVI is obtained by calculating the stiffness parameter  $\beta$ , which indicates the intrinsic stiffness of the blood vessels, CAVI is also theoretically independent of blood pressure. One study reported that there was no significant difference between the KD group without CAL and the control group [37]. CAVI assesses more central vascular stiffness than PVW; therefore, it is speculated that injury to the great vessel may be mild or absent in KD vasculitis. Because CAVI is a relatively new parameter, further studies are needed to elucidate vascular function in patients with a history of KD.

## 6. Conclusion


In patients with a history of KD, the pathogenesis of vascular complications and long-term prognosis are being elucidated by many studies. This suggests an increased risk of atherosclerosis in these populations. However, there are few reports of an increased incidence of atherosclerotic lesions in adult KD patients. Further studies are needed, and careful management of long-term vascular health is required by evaluating vascular function using these clinical tools.

### Author details

Mitsuru Seki  
Department of Pediatrics, Jichi Medical University, Tochigi, Japan

\*Address all correspondence to: m-seki@jichi.ac.jp

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