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# Echocardiography in Kawasaki Disease

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## 1. Introduction

Kawasaki disease is an acute childhood systemic vasculitis characterised by a number of clinical features, with a predilection for damage to the coronary arteries. It predominantly affects children between the ages of 6 months to 4 years, although cases at either extreme of childhood are well described and are recognised to be associated with a greater risk of delayed diagnosis and treatment (Harnden et al., 2009; Pannaraj et al., 2004). There is a male predominance with a male to female ratio of 1.6 to 1. Despite important research progress since its first description in 1967 (Kawasaki, 1967), the aetiology remains unknown and there is no diagnostic test. The timely use of intravenous immunoglobulin has reduced the incidence of coronary artery lesions from 25% to 2-4% (Newburger et al., 2004). Transthoracic echocardiography is recommended in suspected cases of KD, however a normal study does not exclude the diagnosis.

## 2. Incidence

Kawasaki disease is the most common cause of paediatric acquired heart disease (Taubert et al., 1991). The incidence has been rising in both developed (Japan, Korea and United Kingdom) and rapidly industrialising countries such as India, which may reflect both a genuine increase and increased recognition (Krishnakumar & Mathews, 2006). The highest annual incidence is reported in Japan (218 per 100000 children <5 years of age) and Korea (113 per 100000 <5 years) (Nakamura et al., 2010; Park et al., 2011). The incidence is lower in Australia (3.7 per 100000 <5 years) but this data is 15 years old (Royle et al., 1998); given the rising incidence in other countries these rates may be an underestimate of true disease burden. Current epidemiological research is in progress in Western Australia, and these data will provide an updated incidence for Australia children.

## 3. Aetiology

The high incidence of Kawasaki disease in Asian populations and increased risk in families and siblings suggests a genetic predisposition (Fujita et al., 1989; Uehara et al., 2003). Seasonal patterns are well recognised, with peaks in winter and spring in Australia, the United States and Europe and spring to summer peaks in Korea and China (Burgner &

Harnden, 2005). The epidemiology of Kawasaki disease, clustering of cases, community outbreaks and epidemics in the 1980s, support the hypothesis that an unknown infectious agent (or agents) triggers an abnormal inflammatory response in genetically susceptible individuals. Both conventional antigens and bacterial superantigens have been implicated as causative triggers in Kawasaki disease, however the triggering pathogen(s) remain unknown.

#### 4. Pathogenesis

Initially, activated inflammatory cells, particularly monocytes, macrophages, T-cells, and subsequently platelets, adhere to the endothelial cells that line medium-size elastic arteries. Other mediators contribute to destruction of the extra-cellular matrix, leading to vessel dilatation, and subsequent smooth muscle proliferation in the media contributes to later pathology. There is destruction of the intimal layer of the affected artery with inflammatory infiltrate during the acute phase, and histologic findings of myocarditis and fibrosis are found in virtually all cases with Kawasaki disease (Yutani et al., 1981).

#### 5. Clinical assessment

The typical presentation is of an irritable child who has an unremitting high fever (often  $>39^{\circ}\text{C}$ ) for 5 or more days, and some or all classical diagnostic of the clinical features (Table 1). The diagnosis can also be made by experienced clinicians on the fourth day of fever if classical diagnostic criteria are met.<sup>1</sup> In most children the clinical features appear sequentially. Specific features for KD include perineal desquamation and erythema or crusting around the Bacille Calmette Guerin (BCG) inoculation site. Other extracardiac features such as respiratory or gastrointestinal symptoms occur frequently and make the diagnosis difficult.

The diagnosis requires the presence of fever for at least 5 days, and at least four of the following five criteria:

- Polymorphous rash
- Oral mucous membrane involvement, including red fissured lips, strawberry tongue or injected pharynx
- Bilateral non-exudative conjunctivitis
- Changes with extremities including erythema or oedema of palms and soles, or periungual desquamation as a late sign in the subacute phase (~2 or more weeks after illness onset)
- Cervical lymphadenopathy, defined as a unilateral lymph node of  $\geq 1.5\text{cm}$

Table 1. The diagnostic criteria for Kawasaki disease (Newburger et al. 2004)

Incomplete KD should be considered in children who have an unexplained prolonged febrile illness and have not met diagnostic criteria (Newburger et al., 2004). This occurs more commonly in children less than 6 months or greater than 5 years of age, with the younger age group more likely to present with fewer clinical features and also a higher incidence of coronary artery abnormalities (Genizi et al., 2003).

Kawasaki disease shock syndrome has been recently described and is characterised by hypotension and haemodynamic instability, often requiring intensive care. (Dominguez et al., 2008; Yim et al., 2010) These patients may be at increased risk of delayed diagnosis and treatment, refractory disease and more severe coronary artery involvement (Kanegaye et al., 2009).

## **6. Echocardiography in Kawasaki disease**

Transthoracic echocardiography is highly sensitive and specific for the diagnosis of coronary artery involvement and should be performed in confirmed or suspected cases of Kawasaki disease at the time of diagnosis. It is important to ensure that the timing or results of the echocardiogram do not delay initial treatment of Kawasaki disease, and that the diagnosis is made predominantly on clinical findings. On the other hand, if full criteria are not met and coronary artery abnormalities are present on echocardiography, then the child has incomplete features of Kawasaki disease and treatment with high dose intravenous immunoglobulin should be considered. The American Heart Association consensus guidelines provide a schema for the incorporation of echocardiography into the diagnostic process in children with possible incomplete Kawasaki disease (Newburger et al., 2004).

## **7. Principles of echocardiographic assessment**

### **7.1 Optimisation of imaging modalities**

The primary aim of echocardiography is to identify coronary artery involvement, pericarditis and/or myocarditis. As always, optimising machine settings, using the highest possible frequency transducer and reducing two-dimensional gain and compression can achieve better image quality and resolution. B-mode cine loops and still frame images are necessary to assess coronary artery calibre, along with colour Doppler imaging set at a low Nyquist limit for evaluating normal coronary artery diastolic flow. Sedation may be necessary in children who are too irritable to tolerate a detailed study; our preference is to use 50-100mg/kg of chloral hydrate (max 1g) given orally with heart rate and peripheral oxygen saturation monitoring.

### **7.2 Coronary artery assessment**

Coronary arteries should be assessed in multiple imaging planes before a decision is reached about the presence or absence of coronary artery abnormalities. The parasternal short axis view with or without a clockwise rotation of the transducer allows for imaging of the left coronary artery origin, left anterior descending artery and left circumflex artery, as well as the right coronary artery origin and proximal course. Parasternal long axis views with sweeps between the aorta and pulmonary artery will delineate the left main coronary artery, left anterior descending and circumflex arteries. Subcostal views are helpful for assessing the left circumflex artery and the mid-course of the right coronary artery. Apical four chamber views will show the length of the left circumflex artery and distal right coronary artery in the left and right atrioventricular grooves respectively. Coronary artery measurements should be taken from the inner edge to inner edge of the vessel wall and should not be measured at the level of normal branching.

## 8. Cardiovascular involvement

### 8.1 Coronary artery involvement

The main features of coronary artery involvement are dilatation, aneurysm formation, lack of tapering of the distal coronary vessel and perivascular brightness. Aneurysms may be fusiform (spindle-shaped, gradual tapering from normal to dilated segment), saccular (spherical, acute transition from normal to dilated segment), ectatic (uniformly dilated long segment) or segmented (multiple dilatations joined by normal or stenotic areas) (Figure 1). The common sites of coronary involvement (from highest to lowest frequency) include the proximal left anterior descending artery (Figure 2), proximal right coronary artery (Figure 3 & 4), left main coronary artery (Figure 5), left circumflex branch (Figure 5), distal right coronary artery (Figure 6) and the junction of the right and posterior descending coronary artery. Takahashi et al reported that aneurysms were more likely to resolve if they were fusiform in nature and if the child was female and/or less than a year of age. Distal coronary artery aneurysms tended to regress more rapidly than aneurysms located in proximal coronary vessels (Takahashi et al., 1987).

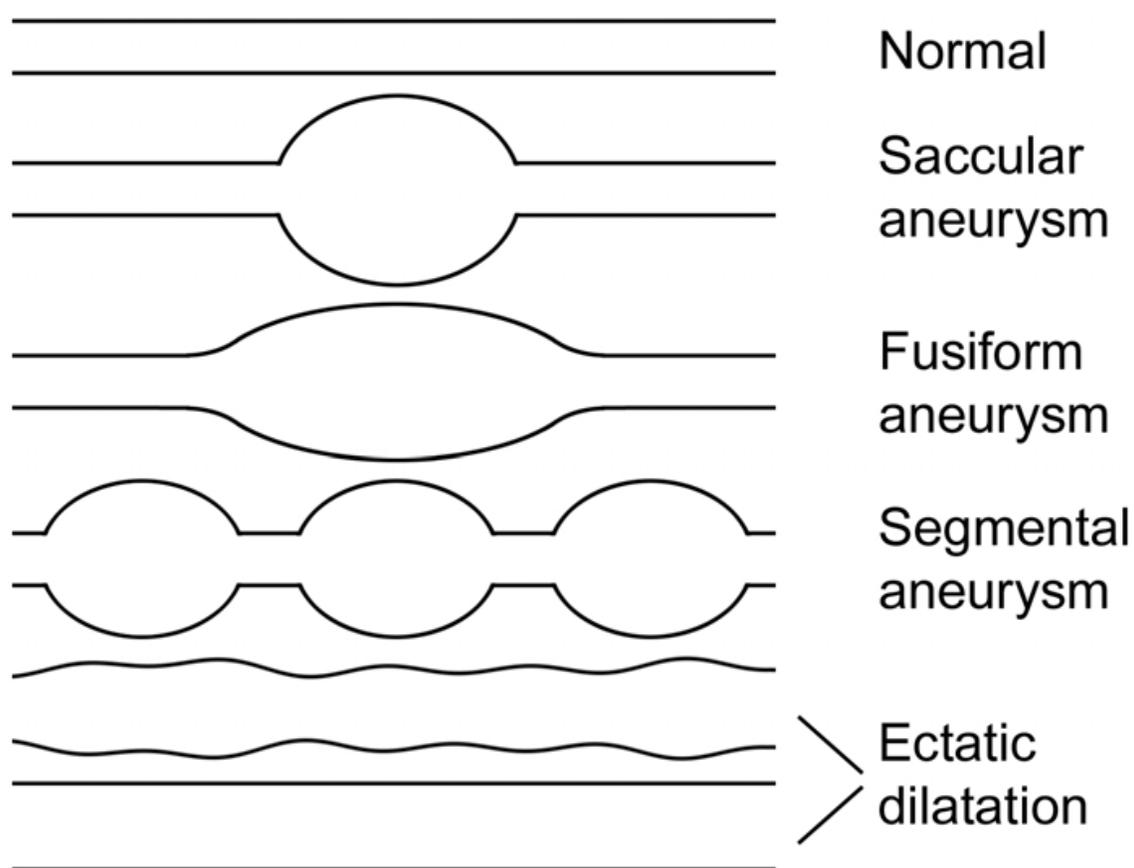


Fig. 1. Illustrative example of coronary artery abnormalities.



Fig. 2. Parasternal short axis echocardiographic image at the level of the mitral valve leaflets demonstrating an aneurysm of the left anterior descending artery.

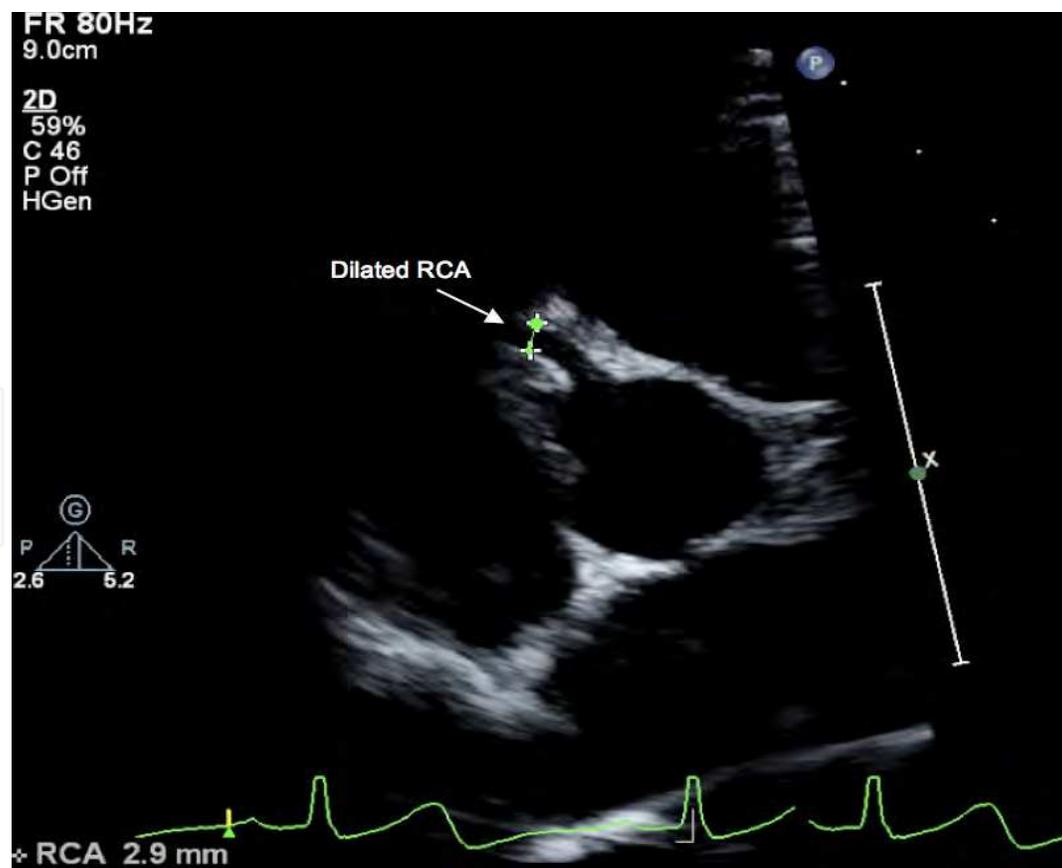


Fig. 3. Parasternal short axis echocardiographic image showing a uniformly dilated proximal right coronary artery (RCA).

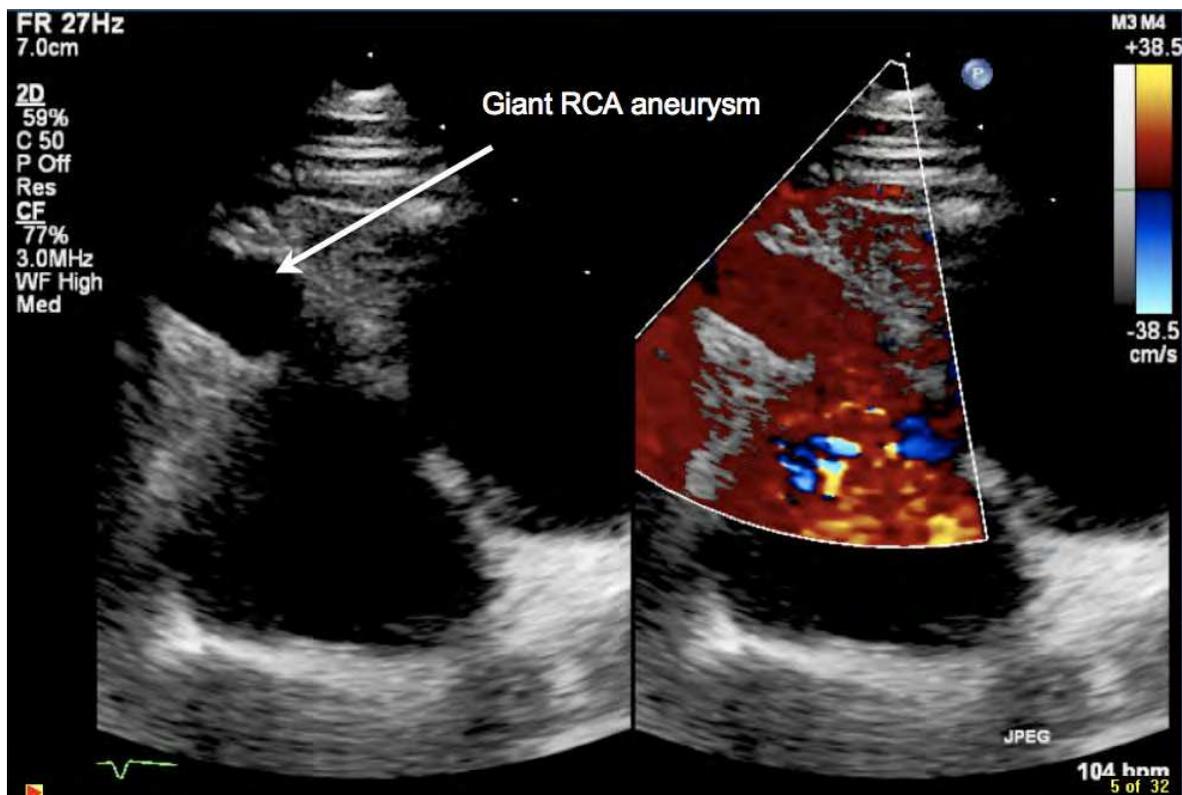


Fig. 4. Parasternal short axis image showing a giant aneurysm of the right coronary artery (RCA).

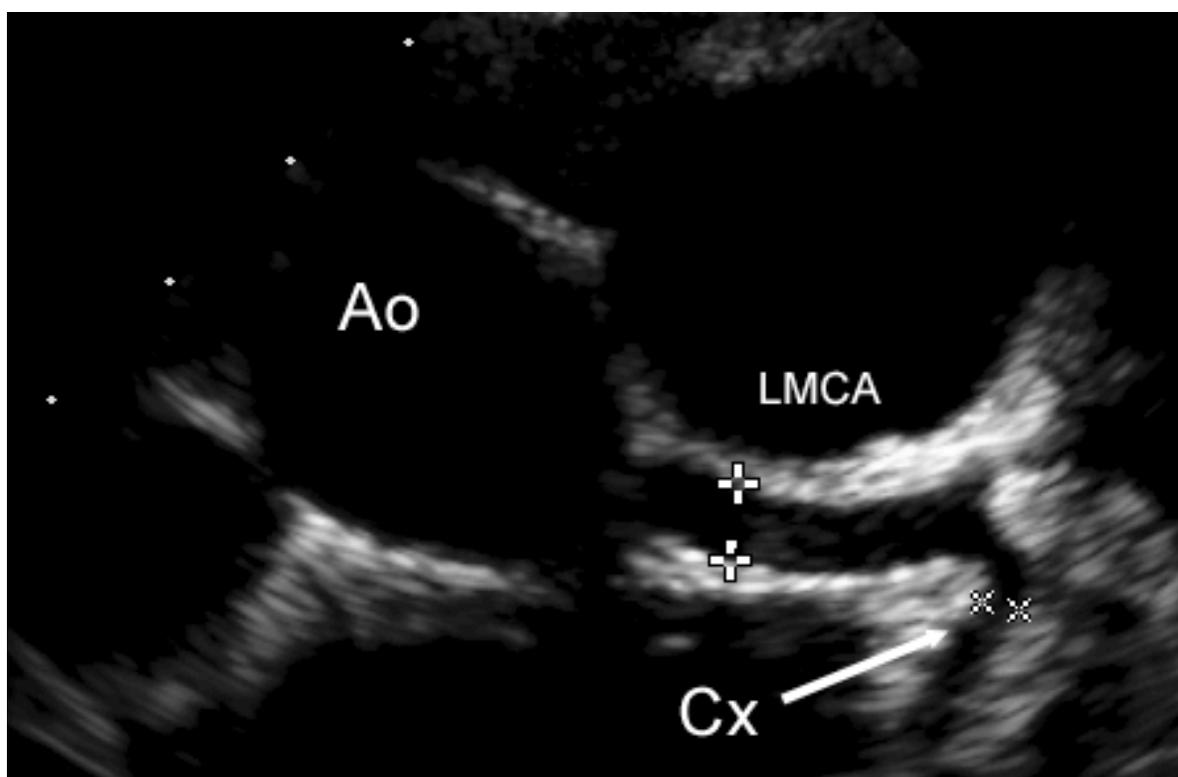


Fig. 5. Parasternal short axis view showing a uniformly dilated left main coronary artery (LMCA, 4.7mm) and dilated circumflex artery (Cx, 3.4mm). Ao = aorta

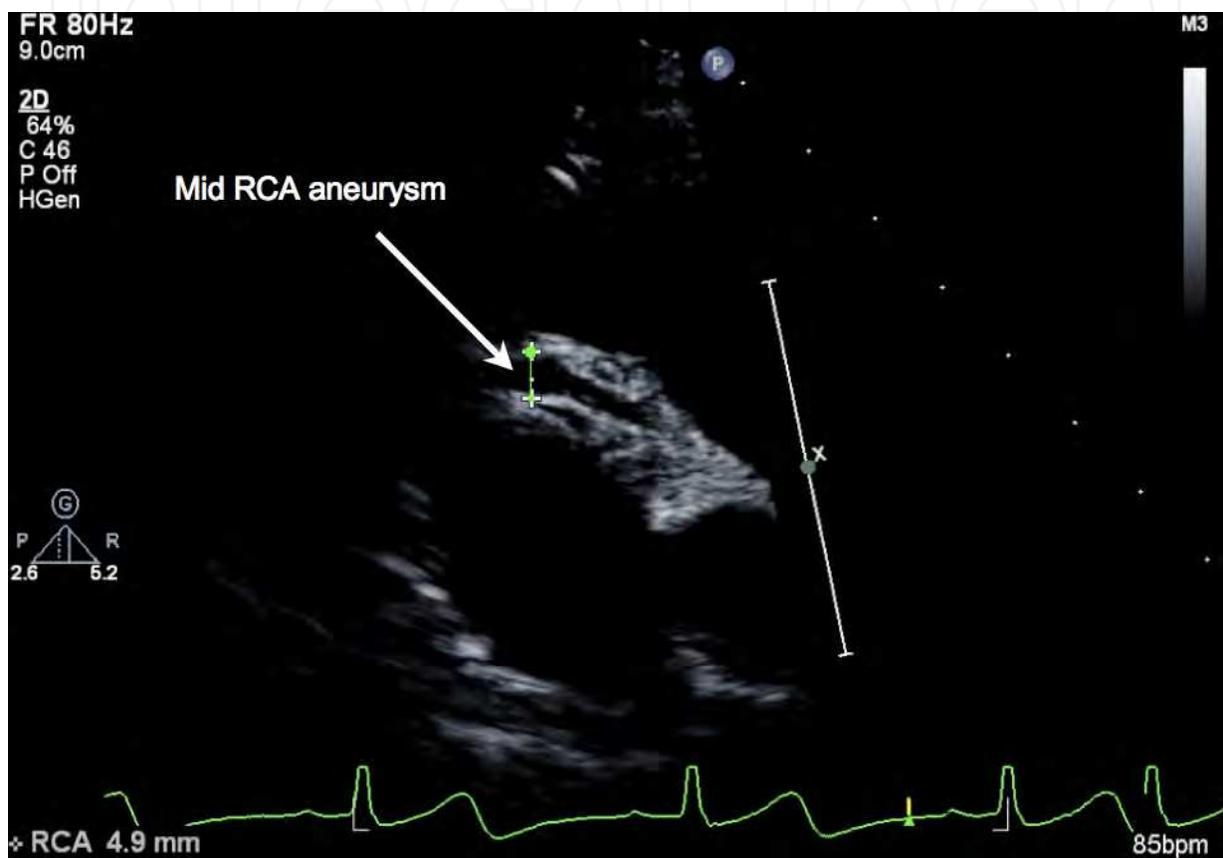


Fig. 6. Off-axis parasternal short axis view demonstrating a fusiform aneurysm of the mid to distal right coronary artery (RCA) aneurysm

## 8.2 Myo-pericarditis

Virtually all patients with Kawasaki disease develop myocarditis to varying degrees during the acute phase, and over half of these patients develop acute transient left ventricular dysfunction (Ajami et al., 2010). Systolic left ventricular function should be routinely assessed. Regional wall motion abnormalities may occur if there is significant coronary artery involvement. Pericarditis may be reflected by the presence of a pericardial effusion.

### 8.3 Valvar involvement

Myocardial inflammation may also involve valve tissue and lead to mitral, tricuspid or aortic regurgitation that is usually mild in nature. If severe mitral regurgitation is present, papillary muscle dysfunction and myocardial ischaemia should be assessed (Akagi et al., 1990). Mild aortic regurgitation is seen to persist in approximately 4% of patients with serial follow-up (Ravekes et al., 2001). Aortic root dilatation may occur as part of the overall vasculitis but is usually mild.

## 9. Timing of echocardiography

The consensus statement from the American Heart Association recommends performing echocardiography at diagnosis, 2 weeks and repeating at 6-8 weeks after the onset of illness for uncomplicated cases. In some centres the 2 week echocardiogram is not routinely performed. The imaging at diagnosis should provide a baseline study for serial follow-up of left ventricular function, coronary arterial involvement, valvar regurgitation, myocarditis and/or a pericardial effusion. The presence of any cardiac involvement warrants closer follow-up. In particular, coronary aneurysms > 5mm in size require close monitoring because of an elevated risk of developing stenotic lesions within the vessel (Mueller, 2009). By 6-8 weeks, transient cardiac involvement is likely to have resolved, or if coronary artery dilation and/or aneurysms are present, the maximum diameter is usually reached by this time.

## 10. Definitions of coronary artery involvement

A number of definitions have been proposed to describe and quantitate coronary artery involvement. The Japanese Ministry of Health classification was first published in 1984. Aneurysms are considered to be small if their internal diameter is <5mm, medium if between 5-8mm, or giant if the internal diameter of the aneurysm is >8mm (Figure 5). These criteria are widely used and define absolute values for coronary artery dimensions and therefore do not account for differences in patient size or the usual caliber of different coronary artery branches. The American Heart Association AHA guidelines were published in 2004 and define coronary artery dimensions with respect to body surface area, which requires both weight and height measurements. These define a coronary artery as dilated if the intra-luminal diameter has a z-score of  $\geq 2.5$ . Manlhiot et al. recently proposed a revision of this classification to account for differences in body size and caliber of coronary artery branches, and report that coronary artery abnormalities are small if the z-score is  $\geq 2.5$  to <5, large if the z-score is  $\geq 5$  to < 10, and giant if the z-score is  $\geq 10$  (Manlhiot et al., 2010). This method is however prone to significant variation in the calculated z-score with minor variation in measurement of coronary size. It is therefore too early to determine whether this classification will be widely employed.

## 11. Further imaging modalities

As the difficulty of coronary artery imaging increases with age, further imaging options may be necessary. Even in experienced hands, echocardiography also has its limitations in detecting stenosis and thrombosis. The efficacy of other non-invasive imaging modalities such as magnetic resonance imaging and multi-detector computed tomography has been increasingly evaluated for coronary artery assessment in Kawasaki disease (Figure 7).



Fig. 7. Magnetic resonance image using T2 weighted truFISP sequence demonstrating a dilated left anterior descending (LAD) artery with a distal fusiform aneurysm.

## 12. Functional assessment

Cardiac stress testing may be used to identify reversible ischaemia and regional wall motion abnormalities during increased demand. Coronary perfusion abnormalities can be further assessed with exercise echocardiography, pharmacologic (dobutamine, dipyridamole or adenosine) stress echocardiography and exercise myocardial perfusion scans. The stress modality employed depends on the age of the child and local expertise, although practically speaking, pharmacologic stress echocardiography or exercise myocardial perfusion scans are the preferred techniques in the paediatric age group. If abnormalities of coronary segmental perfusion are found, the results may assist decision-making for further management.

### 13. Cardiac catheterisation

Cardiac catheterisation with selective coronary angiography is considered the gold standard for delineation of coronary artery anatomy, and if required interventional procedures such as balloon angioplasty, stent placement or percutaneous transluminal coronary revascularisation may be performed in the same setting. Cardiac catheterisation is generally not recommended for patients with mild coronary artery involvement, however it can provide useful detailed information and help with risk stratification of patients who have complex coronary artery lesions (Figure 8 & 9). Coronary angiography in this instance is recommended 6-12 months after the onset of Kawasaki disease, or sooner as clinically indicated.



Fig. 8. Lateral selective coronary angiogram demonstrating a significantly dilated left anterior descending (LAD) artery and proximal circumflex (Cx) artery.

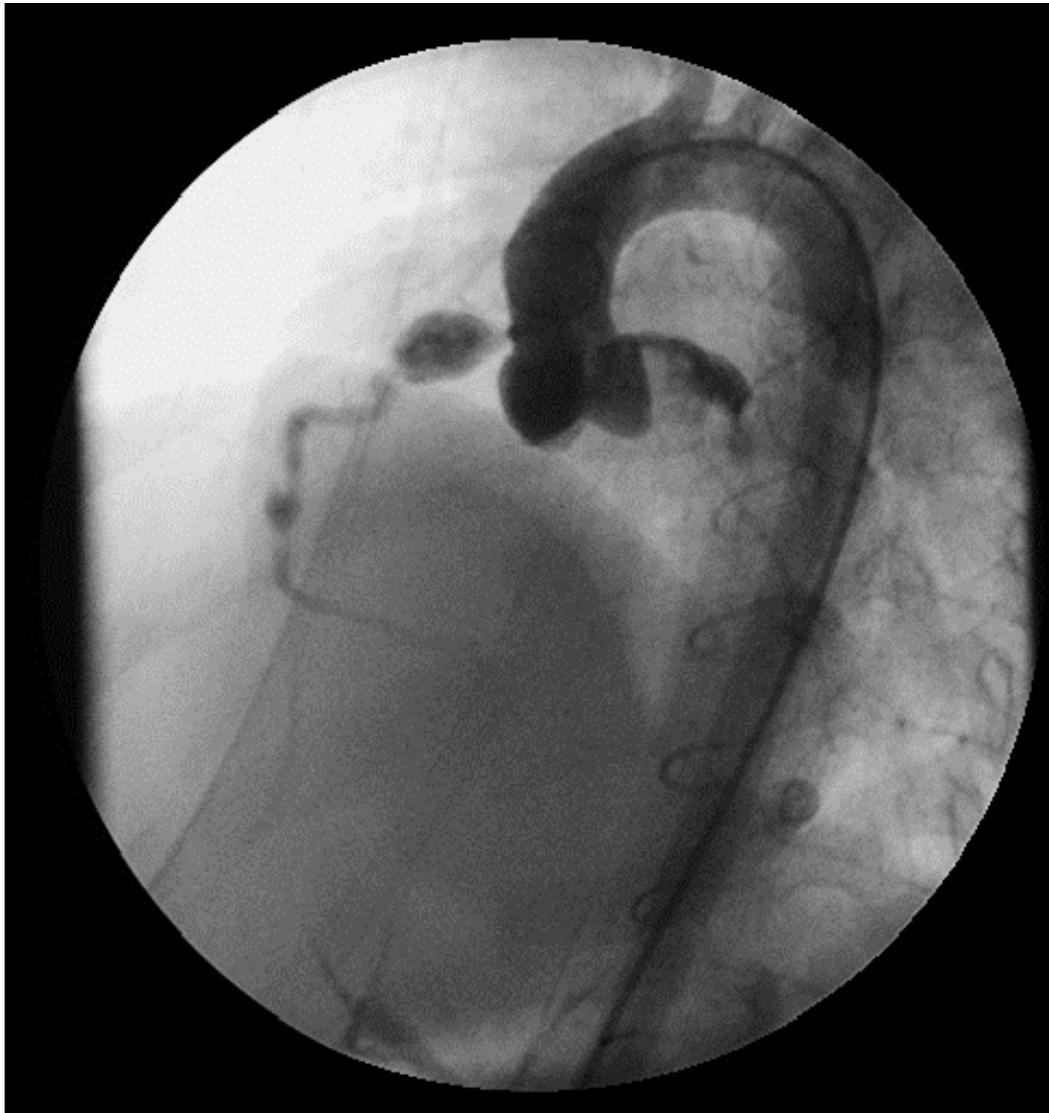


Fig. 9. Lateral angiographic plane with injection of contrast in the ascending aorta via a pigtail catheter, showing large saccular aneurysms in both the proximal right and left coronary arteries. (Image courtesy of Professor Mike South, Royal Children's Hospital, Melbourne)

#### 14. Natural history

The percentage of patients developing coronary aneurysms is reduced with timely administration of intravenous immunoglobulin. Nearly 50% of those coronary artery aneurysms will show angiographic regression within 1 to 2 years following the illness, with smaller lesions having a greater chance of resolution (Newburger et al., 2004). The size of the aneurysm is a major predictor for the development of myocardial infarction (Yeu et al., 2008). As aneurysms remodel with time, however, the risk of coronary artery stenosis increases.

There is evidence that Kawasaki disease in childhood may increase the risk of cardiovascular disease in adulthood. Patients with coronary artery aneurysms have an increase in carotid artery intima-media thickness, and increased systemic arterial stiffness with higher pulse wave velocities (Cheung et al., 2007; Ooyanagi et al., 2004; Suzuki et al., 1996). Furthermore there are data demonstrating abnormal vascular endothelial function and lipid profiles in patients. The exact level of increased risk is uncertain.

## 15. Follow-up recommendations

Patients with Kawasaki disease should be followed up based on risk stratification according to the severity of coronary artery involvement in consultation with a paediatric cardiologist familiar with managing the condition.

- **Kawasaki disease is a common childhood systemic vasculitis characterized by specific clinical features and persistent fever for at least 5 days.**
- **Transthoracic echocardiography is recommended in suspected cases of Kawasaki disease, however a normal study does not exclude the diagnosis.**
- **Treatment with high dose intravenous immunoglobulin should be initiated based on the clinical presentation, and should not be delayed by the timing of echocardiography.**
- **The aims of echocardiography are to identify coronary artery dilatation and aneurysms, valvar regurgitation, myocarditis with ventricular dysfunction and pericarditis with effusion.**
- **Echocardiography should be performed at diagnosis, and approximately 6-8 weeks after the onset of illness, with more frequent assessments required if cardiac involvement is present.**

Table 2. Kawasaki disease - Summary points

## 16. Conclusion

In summary, Kawasaki disease is an important and common systemic vasculitis of childhood, and the advent of intravenous immunoglobulin has significantly reduced, but not removed the risk of abnormal coronary artery development in affected individuals. There have been significant advances in our overall understanding of the condition, although the aetiology remains uncertain. Of concern is the emerging evidence that KD is a risk factor for adult coronary artery disease. Further research into pathogenesis and long term outcomes are required.

## 17. Acknowledgements

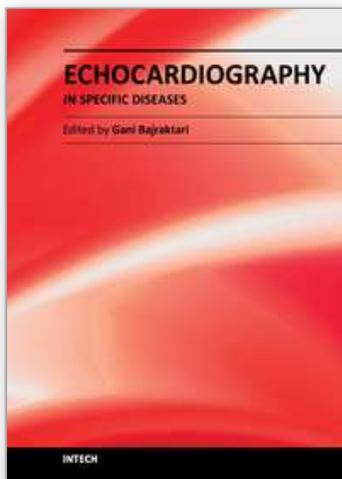
We would like to thank Professor Mike South for his contribution of catheterisation images, and Dr Adam Doyle for the coronary artery illustration.

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The book "Echocardiography - In Specific Diseases" brings together contributions from well-known researchers from around the world, some of them specialized in imaging science in their clinical orientation, but also representatives from academic medical centers. Each chapter is structured and written to be accessible to those with a basic knowledge of echocardiography but also to be stimulating and informative to experts and researchers in the field of echocardiography. This book is primarily aimed at cardiology fellows during their basic echocardiography rotation, fellows of internal medicine, radiology and emergency medicine, but also experts in echocardiography. During the past few decades technological advancements in echocardiography have been developing rapidly, leading to improved echocardiographic imaging using new techniques. The authors of this book tried to explain the role of echocardiography in several special pathologies, which the readers may find in different chapters of the book.

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