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SPECIAL ISSUE – KAWASAKI DISEASE

The role of echocardiography in Kawasaki disease

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Abstract

Kawasaki disease (KD) is an acute, self-limited vasculitis affecting young children. It can result in coronary artery abnormalities in a significant proportion of patients, especially if the diagnosis is missed or treatment gets delayed. Echocardiography is the imaging modality of choice for detection of coronary artery abnormalities and assessment of myocardial function. It is also useful for characterization and risk stratification of patients with KD. Echocardiography should be performed at the time of diagnosis and then again at 1–2 weeks and 4–6 weeks after treatment, for uncomplicated cases who do not have significant coronary artery involvement. Use of a standardized imaging protocol is necessary to detect and characterize coronary artery abnormalities, including standardization of measurements (Z scores). For patients with evolving abnormalities, more frequent assessment is necessary in order to detect thromboses in aneurysms. Long-term prognosis and management is dependent on both the maximal and current Z scores of aneurysms. Patients with large or giant aneurysms (i.e., Z score ≥ 10) are at the highest risk of both thrombosis and stenosis. Such patients need careful follow-up for subsequent cardiovascular events. Many of them would be candidates for advanced cardiovascular imaging and may require revascularization therapy. Serial echocardiography plays a key role in surveillance. In addition, stress echocardiography has proven useful as a modality to assess for inducible myocardial ischemia. Intravascular ultrasound has been recommended for functional and structural assessment of coronary arteries in children with KD.

Key words: coronary arteries, coronary artery aneurysms, echocardiography, intravascular ultrasound, Kawasaki disease, stress echocardiography.

The role of any cardiovascular imaging modality used in the setting of Kawasaki disease (KD) is to diagnose and characterize cardiac and coronary artery involvement and related evolving complications. While KD is characterized by an acute self-limited vasculitis, a pancarditis may affect the pericardium (leading to pericardial effusions), endocardium (leading to valvulitis and valvar regurgitation) and myocardium (leading to myocarditis and both systolic and diastolic ventricular dysfunction). The vasculitis affects medium-sized arteries, predominately the coronary arteries, and while the majority of patients will have either no involvement or transient dilation, a distinct pathologic process leading to aneurysm formation has been defined.[1] During the acute illness, a necrotizing arteritis destroys the vascular architecture and, under hydrostatic pressure, affected areas may become aneurysmal and, in rare and severe cases, are at risk for rupture. Thrombosis is an important concern, given flow stasis, endothelial disruption and dysfunction, and thrombocytosis. Resolution of the acute inflammatory process may be followed by chronic vasculitis and luminal myofibroblastic proliferation, which may normalize luminal dimensions, reducing the risk of thrombosis, but increasing the risk of stenoses and arterial dysfunction. Coronary artery complications are the primary cause of morbidity and mortality related to KD, and have become the leading form of acquired heart disease in children from developed countries.

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ECHOCARDIOGRAPHY STANDARDS

Echocardiography is the mainstay of cardiovascular assessment in KD, particularly during the acute illness, but also during long-term follow-up, due to its non-invasive nature and good sensitivity and specificity in identifying and characterizing cardiac and coronary artery abnormalities. Complete assessment includes characterization of ventricular function and wall motion (particularly the left ventricle), characterization of any valvar regurgitation (particularly the mitral and aortic valves), and subjective quantification and hemodynamic impact of any pericardial effusion.

For the coronary arteries, a standardized imaging protocol performed under the supervision of an experienced pediatric echocardiographer is required for accurate and complete assessment, including obtaining a specific sequence of imaging views in order to delineate all segments of the coronary arteries (Table 1).[2] Imaging conditions should be maximized, and sedation of young or uncooperative children is often needed. A high-frequency transducer should be used to optimize resolution. Coronary artery luminal diameters should be measured from inner edge to inner edge in all segments, avoiding points of branching. Aneurysms should be measured in all dimensions, and the dimensions, shape, number and location recorded, as well as the presence of any intraluminal thrombus and flow disturbance. For multiple aneurysms in series in a branch, the diameter of any intervening segment should be noted.

Table 1 Echocardiographic views of coronary arteries in patients with Kawasaki disease†

Left main coronary artery
Precordial short axis at level of aortic valve
Precordial long axis of left ventricle (superior tangential)
Subcostal ventricular long axis
Left anterior descending coronary artery
Precordial short axis at level of aortic valve
Precordial superior tangential long axis of left ventricle
Precordial short axis of left ventricle
Left circumflex branch
Precordial short axis at level of aortic valve
Apical four-chamber
Right coronary artery, proximal segment
Precordial short axis at level of aortic valve
Precordial long axis (inferior tangential) of left ventricle
Subcostal coronal projection of right ventricular outflow tract
Subcostal short axis at level of atrioventricular groove
Right coronary artery, middle segment
Precordial long axis of left ventricle (inferior tangential)
Apical four-chamber
Subcostal left ventricular long axis
Subcostal short axis at level of atrioventricular groove
Right carotid artery proximal (#1) and mid (#2) are observed in the atrioventricular groove from the third intercostal space at the left and right sternal border
Right coronary artery, distal segment
Apical four-chamber (inferior)
Subcostal atrial long axis (inferior)
Posterior descending coronary artery
Apical four-chamber (inferior)
Subcostal atrial long axis (inferior)
Precordial long axis (inferior tangential) imaging
Posterior interventricular groove

†From McCrindle BW, Rowley AH, Newburger JW, *et al.* (2017) Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* **135** (17), e927–99.

CHARACTERIZATION OF CORONARY ARTERY INVOLVEMENT

In addition to defining qualitative aspects of the coronary arteries and aneurysms, quantitative assessment is particularly important for classification of involvement, which is an important prognostic factor and defines management algorithms. Initial classification schemes relied on absolute luminal diameters, with no adjustment for the size of the patient. It is now standard of care to convert dimensions to Z scores based on patient size, specifically body surface area. Z score equations have proliferated, from simple linear regression to more complex non-linear statistical models (Table 2),[2] and have been derived from normal populations of varying size and race, which can impact the Z score.

To demonstrate, a typical 6-month-old with a diameter 2.5 mm of the proximal left anterior descending branch would have a significantly elevated Z score of +4.23 using McCrindle,[6] +2.95 using Dallaire,[8] and +3.30 using Kobayashi[9] systems. A typical 5-year-old with the same dimension of 2.5 mm would have a normal Z score of +1.65 using McCrindle, +1.43 using Dallaire, and +1.60 using Kobayashi. The Kobayashi system is based on the largest number of normal children, provides sex-specific models as well, and is available as an online calculator (http://raise.umin.jp/zsp/calculator). The choice of Z score system to use is a matter of both debate and preference, but might be influenced by the rigor of the study and the race of the patient at hand. One precaution in using Z scores is that, particularly for small patients, small errors in measurement of

Table 2 Z score methods for normalizing coronary artery luminal dimensions from echocardiography†

Principal author	De Zorci[3]	Kurotabi[4]	Tan[5]‡	McCrindle[6]	Olivieri[7]	Dallaire[8]	Kobayashi[9]
Year of publication	1997	2002	2003	2007	2009	2011	2016
Number of subjects	89	71	390	221	432	1036	3851
Country	USA	Japan	Singapore	USA	USA	Canada	Japan
Regression method for model fitting of BSA	Linear	Linear	Linear	Exponential	Logarithmic	Square root	LMS
BSA calculation method	NS	NS	NS	Haycock	Dubois	Haycock	Haycock
Values for left circumflex	No	No	No	No	No	Yes	Yes

†Adapted from McCrindle BW, Rowley AH, Newburger JW, *et al.* (2017) Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* **135** (17), e927–99. ‡Age range limited to 2 months to 8 years; also provided for age, gender, and to the aortic annulus. BSA, body surface area; LMS, lambda-mu-sigma.

the coronary artery diameter, patient weight or height may lead to important variations in Z score. In addition, the presence of fever may have a small impact in increasing coronary artery dimensions, although less so than that due to KD, and usually not enough to affect the accuracy of classification.[10,11]

Z scores give a continuous measure of coronary artery involvement, from which patients can both be classified and followed longitudinally for changes accounting for patient growth. Classification can now be based solely on maximal coronary artery Z score (Table 3).[2] The majority of patients with KD will have normal Z scores, or dilation which is inevitably transient. A subset of patients with presumed dilation may actually have normal variations in coronary artery anatomy, often of the left main coronary artery, or dominance of the right or left coronary artery. These patients become evident when dimensions do not return to normal during follow-up. Another subset of patients will have a normal Z score initially, which then decreases with follow-up. These patients might also be considered to have had mild dilation related to either fever or KD, or measurement error. Patients with a maximal Z score greater than +2.5 are considered to have an aneurysm(s), and the greater the Z score, the greater the damage to the arterial architecture from the necrotizing arteritis during the acute illness.

Table 3 Risk classification of coronary artery abnormalities during follow-up†

1 No involvement at any time point (Z score always < 2)
2 Dilation only (Z score 2 to < 2.5)
3 Small aneurysm (Z score ≥ 2.5 to < 5)
- 3.1 Current or persistent
- 3.2 Decreased to dilation only or normal luminal dimension

4 Medium aneurysm (Z score ≥ 5 to < 10, and absolute dimension < 8 mm)
- 4.1 Current or persistent
- 4.2 Decreased to small aneurysm
- 4.3 Decreased to dilation only or normal luminal dimension

5 Large and giant aneurysm (Z score ≥ 10, or absolute dimension ≥ 8 mm)
- 5.1 Current or persistent
- 5.2 Decreased to medium aneurysm
- 5.3 Decreased to small aneurysm
- 5.4 Decreased to dilation only or normal luminal dimension

†From McCrindle BW, Rowley AH, Newburger JW, *et al.* (2017) Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* **135** (17), e927–99.

ROLE OF ECHOCARDIOGRAPHY IN KD DIAGNOSIS

Patients should have initial echocardiography performed when the diagnosis of KD is considered. Treatment should not be delayed if this cannot be performed. For patients with incomplete KD who do not have sufficient clinical criteria, the presence of coronary artery dilation or aneurysms, or the presence of ventricular dysfunction, mitral valve regurgitation and pericardial effusion on echocardiography are satisfactory to confirm the diagnosis. While there have been reports of coronary artery perivascular brightness in patients during the acute illness, this is considered an unreliable and non-specific indicator and not sufficient for diagnosis. A normal echocardiogram obtained very early in the illness does exclude the diagnosis of KD.

ROLE OF ECHOCARDIOGRAPHY DURING THE ACUTE KD ILLNESS

The findings of the initial echocardiogram at the time of diagnosis determine the frequency of repeat assessment. For patients with coronary artery Z scores that are normal or indicate dilation only, and who have no other important cardiac findings, repeat echocardiography is recommended within 1–2 weeks and again at 4–6 weeks after treatment.[2] However, for patients with Z scores greater than +2.5 more earlier and more frequent assessment may be required, at least until Z scores have stopped increasing. Patients with large or giant aneurysms are of particular concern, since they have a high risk of thrombosis. Failure to escalate thromboprophylaxis in the face of expanding aneurysms can be an important cause of morbidity and mortality. Increased surveillance may entail performing echocardiography twice per week while the Z scores are increasing, and then weekly for the first 45 days. The ability of echocardiography to adequately detect thrombosis is unclear, but the use of a wider gray scale may be helpful.

ROLE OF ECHOCARDIOGRAPHY DURING LONG-TERM FOLLOW-UP

Classification depends on maximal Z score of any branch as noted during or shortly after the acute illness, but then is further refined by reductions in Z scores as the patient is followed long-term. Patients with normal Z scores or transient dilation only do not require long-term follow-up beyond 4–6 weeks. For patients with aneurysms, prognosis and risk stratification also should take into account both the maximal and current Z score of any aneurysm, together with additional features, such as the shape and location of the aneurysm, the branch(es) involved, the number of aneurysms in a branch and in total, and luminal irregularities in intervening segments. The pathologic processes of chronic inflammation and luminal myofibroblastic proliferation, together with laminar thrombosis on the wall of aneurysms, lead to reduction in luminal dimensions which may progress to stenosis. In addition, there is an ongoing risk of luminal thrombosis, which is greatest in those patients with large or giant aneurysms. The larger the aneurysm, the greater the risk of both thrombosis and stenosis, and the less likely are reductions in luminal dimensions to occur or to be reassuring. Cardiovascular events are rare in patients who do not have large or giant aneurysms.

The frequency of echocardiography during long-term follow-up depends on the patient's risk classification. Patients with aneurysms that reduce to a Z score less than +2.5 require infrequent ongoing follow-up, but echocardiography may be omitted. For those with persistent aneurysms, echocardiography should still be performed, with particular attention to thrombosis and to ventricular wall motion abnormalities. Given the constant risk of stenoses, the periodic assessment for inducible myocardial ischemia takes on importance, particularly for those with large or giant aneurysms. Stress echocardiography has a prominent role.

SPECIALIZED APPLICATIONS OF ECHOCARDIOGRAPHY AND VASCULAR ULTRASOUND

Stress imaging for inducible myocardial ischemia is an integral part of the follow-up of KD patients with aneurysms. Stress echocardiography is used to identify myocardial segments with inadequate coronary arterial blood supply due to coronary lesions. The increase in heart rate during stress imaging produces an increase in myocardial oxygen demand. With the presence of stenotic coronary artery branches, wall motion abnormalities will be observed in the myocardial segments supplied by the stenotic arteries. For patients with myocardium at risk of ischemia, wall motion abnormalities at stress appear earlier than electrocardiographic changes or elevations of cardiac enzymes.

Stress echocardiography can be performed with the use of either physiologic exercise, such as treadmill or bicycle, or a pharmacologic agent, such as dobutamine. Both exercise and dobutamine have been used for stress echocardiography for patients with KD. However, despite the fact that exercise represents a more physiologic stressor, the majority of published reports have used dobutamine for stress. Using dobutamine stress, Pahl *et al.* studied 28 children with previously documented coronary artery abnormalities, two of whom showed stress-induced wall motion abnormalities and subsequently had a positive angiography for critical stenosis of the left anterior descending coronary artery.[12] Henein *et al.* evaluated longitudinal ventricular function during exercise in children with KD, and noted a reduction in global longitudinal function compared to normal controls.[13] Noto *et al.* performed the largest study of 50 children with KD evaluated with angiography and dobutamine stress echocardiography.[14] Angiograms documented the presence of > 50% stenosis of one of the major coronary artery branches in 21 children, 19 of whom also had corresponding wall motion abnormalities on stress echocardiography. None of the patients with a negative angiogram had a positive dobutamine stress echocardiogram. In this study, dobutamine stress echocardiography had sensitivity and specificity of 90% and 100%, respectively, for detection of coronary artery stenosis. In a further study, Noto *et al.* defined the prognostic value of dobutamine stress echocardiography for follow-up.[15] Dobutamine stress echocardiography had sensitivity and specificity of 94.4% and 82.5%, respectively, for detection of coronary artery lesions at the beginning and 93.7% and 95.4%, respectively, at 15 years of follow-up. The limitations of using dobutamine for stress are that it is not physiologic and is uncomfortable for patients. For exercise stress, the potential use of new ergometers, such as semi-supine ergometers, allow continuous imaging acquisition during exercise and may increase feasibility and accuracy. However, its use is limited to older patients who fit and can cooperate with the exercise protocol.

The thickening of the arterial wall through thrombosis and luminal myofibroblastic proliferation leads to reduction of luminal dimensions, reducing the risk of thrombosis but increasing the risk of stenoses. Characterization of the arterial wall may provide important prognostic information in the long-term follow-up of patients with aneurysms. Intravascular ultrasound uses thin ultrasound probe catheters inserted into the coronary artery lumen, and has been used for the evaluation of coronary artery plaque, lumen and vessel dimensions in the setting of atherosclerotic coronary artery disease.[16] Since it is invasive, often conventional angiography is performed at the same time. For patients with KD, intravascular ultrasound has the potential of identifying the location and severity of arterial wall abnormalities, but also offers a functional assessment of the coronary artery as well. Iemura *et al.* used intravascular ultrasound combined with intracoronary infusions of acetylcholine and isosorbide dinitrate to evaluate wall morphology and function of persistent and regressed coronary artery aneurysms in patients with a history of KD.[17] They were able to demonstrate intimal thickening of the arterial walls and, with the acetylcholine and isosorbide dinitrate infusion, were also able to demonstrate an abnormal increase in vascular constriction and reduction in vasodilation properties in aneurysmal segments, indicating abnormal arterial function. Mitani *et al.* used intravascular ultrasound to characterize quantitatively and qualitatively the arterial wall of coronary artery lesions, and compared this to conventional angiographic findings in adolescents and young adults after KD.[18] They interpreted their findings to suggest that coronary artery lesions have atheroma-like features, and that intravascular ultrasound-based 'virtual histology' might become a gold standard against which emerging non-invasive imaging modalities that may also characterize the arterial wall might be assessed. These small studies, together with recent reports using optical coherence tomography, suggest that arterial wall characterization is possible for patients after KD, although its utility in terms of refining prognosis requires further study.

SUMMARY

Echocardiography is the mainstay of imaging of cardiovascular involvement related to KD. Complete characterization of coronary artery involvement is necessary, including quantitative assessment as Z scores, to ensure proper prognostication and calibration of follow-up surveillance and treatment. Both stress echocardiography and intravascular ultrasound provide further risk stratification for those patients with important coronary artery aneurysms.

CONFLICTS OF INTEREST

None.

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