Review Article

Echocardiographic Evaluation in Kawasaki Disease

CME Credits

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Abstract

Kawasaki disease (KD) is an etiology-unknown but with a generalized inflammatory disorder of multiple organs and systems in childhood. The basic pathologic changes are panvasculitis of the small and medium-sized arteries, mainly the coronary arteries. It is now the leading cause of acquired heart disease during childhood in developed countries and has led to the early development of angina pectoris, myocardial ischemia/infarction, and even sudden cardiac death in early adulthood. Although there is no definitive diagnostic test for KD, the accurate diagnosis is dependent on the clinical presentations to meet the diagnostic criteria. Echocardiography is a well-known noninvasive tool to detect structural abnormalities and evaluation of cardiovascular function. It has been reported to detect accurately the early and late cardiovascular abnormalities, including perivascular brightness, lack of tapering, dilatation, and aneurysmal formation of coronary arteries as well as the mitral/aortic regurgitation, pericardial effusion, and myocardial functional changes in KD. In cases of incomplete form of KD and patients whose clinical manifestations did not meet the diagnostic criteria, abnormal echocardiographic findings of coronary artery may provide the assistance for early diagnosis of KD. Long-term periodic echocardiographic follow-up is the basic and essential study for patients of KD with initial coronary arterial abnormalities. Ninety nine articles that studied echocardiographic findings of KD had been reviewed and will be discussed.

Keywords: Coronary arterial aneurysm, coronary arterial lesions, Kawasaki disease, Kawasaki syndrome, pericardial effusion, pericarditis, stress echocardiography, three-dimensional real-time echocardiography, ventricular dysfunction

Introduction

Kawasaki disease (KD) is an acute inflammatory disease of multiple organs and systems in childhood. The inflammatory disorder affects mainly the small and medium-sized arteries, and results in panvasculitis and pancarditis in infants and children.[1-3] It is now the leading cause of acquired heart disease of children in developed countries. It commonly affects in children younger than 5 years old with most common in small children between 2 and 3 years old and with male predominance.[4] The estimated incidence of KD is about 20 in 100,000 children. The highest incidence of 134 in 100,000 among Japanese children aged < 5 years, followed by 86.4 in 100,000 in Korean children and then by 66/100,000 in Taiwanese children.[3,5-7] The etiology of KD is still unknown, although some specific genetic markers, specific infections, and immunological responses have been reported to be the possible causes of this particular disease. The main cardiovascular manifestations of KD are pancarditis, which may lead to pericardial effusion, valvulitis, valvular regurgitation, myocarditis, myocardial dysfunction, and panvasculitis, which is usually involving the coronary arteries. The most commonly involved artery is coronary artery (CA), which results in aneurysmal dilatation during acute and subacute stages. Due to the acute inflammatory and necrotizing changes of coronary arteritis, the vascular architecture was destroyed, and the coronary arteries became dilatation and aneurysmal formation due to the hydrostatic pressure.[8] These aneurysmal changes of CA visualized by two-dimensional echocardiography (2 DE) had been reported as early as 1979 by Yoshida *et al*.[9] They found 4 KD patients presented with larger echo-free spaces of the linear echo-free structure arising from the aortic root by cross-sectional echocardiography. Those larger echo-free spaces were identified as CA aneurysms

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Abbreviations

AHA	American Heart Association
CA	Coronary artery
CEDi	Coronary external diameter index
IVIG	Intravenous gamma globulin
IVUS	Intravascular ultrasound echocardiography
JMH	Japanese Ministry of Health
KD	Kawasaki disease
RT-3DE	Real-time three-dimensional echocardiography
2 DE	Two-dimensional echocardiography
VGH	Veterans General Hospital Taipei

later by coronary angiography or autopsy.[9] They concluded that the cross-sectional echocardiographic technique is a useful noninvasive diagnostic method for imaging the coronary arteries and aneurysms in KD.[9,10] After that time, Yoshikawa *et al*. and Hiraishi *et al*. reported separately the noninvasive visualization of coronary arterial aneurysms in KD by cross-sectional echocardiography.[11,12] Besides spontaneous regression of the arterial dilatation with normalization of the coronary lumen by myofibroblastic proliferation, thrombosis formation in the aneurysms and then stenosis and calcification of the involved CA are the long-term complications.[13] These CA changes are the causes of morbidity and mortality of KD patients who experienced myocardial ischemia, infarction, sudden death, and congestive heart failure at a late time. Echocardiography has been reported as a noninvasive and accurate diagnostic tool for diagnosis and long-term evaluation of the changes in CA lesions and the functional status of the cardiovascular system. It can characterize cardiac and CA involvement and related complications. The echocardiographic definition of CA abnormalities in KD was used to be proposed by the Japanese Ministry of Health (JMH) in 1984.[2] These criteria included: If the internal lumen diameter is >3.0 mm in children <5 years of age or >4.0 mm in children above 5 years of age if the internal diameter of a segment measures at least 1.5 times that of the adjacent segment, or if the CA lumen is clearly irregular.[2,3] The other suggestive echocardiographic features in KD were perivascular brightness, lack of tapering of CA, decreased left ventricular function, mitral regurgitation, and pericardial effusion.[3] Early echocardiographic evaluation of CA has been reported to be helpful for the early accurate diagnosis even without meeting the diagnostic criteria of KD in the small infants. During the acute stage, about 15%–25% of untreated KD patients may present with CA lesions, which may cause the morbidity and mortality of KD.[13] The incidence of CA lesions decreases to about 2%–7% in KD patients whom had been treated appropriately with higher doses of Aspirin, Intravenous gamma globulin (IVIG) with/without steroid.[14] Those CA lesions need usually a serial echocardiographic studies to help the early diagnosis of KD. Hörl *et al*. studied 124 patients with KD, they found that 24 (26%) children had serial echocardiography to detect the significant increase in diameters of CA and then to confirm the diagnosis.[15] Periodic echocardiographic examination is necessary to evaluate the changes in cardiac structure, function, and also the changes in internal diameters of CA. In this review, the cardiovascular changes, including the CA lesion, cardiac function, mitral valve, aortic valve, and pericardium during acute, subacute stages, and long-term follow-up of KD will be presented and discussed.

Echocardiographic Role in Early Diagnosis of Typical and Incomplete Kawasaki Disease

Since the actual etiology of KD is not completely understood, the standard diagnostic method of KD is dependent on the meet of Diagnostic Criteria, which was adopted from the guidelines of the American Heart Association (AHA), including fever plus ≥4 of 5 principal clinic signs.[2,3] Not all the patients, especially the younger infants with prolonged fever and suspected KD who do not fulfill meeting the diagnostic criteria of KD may have a high risk of cardiovascular complications.[16] Early abnormal echocardiographic findings may be helpful for the diagnosis of incomplete KD and also to identify the patients with the possibility of resistance to IVIG.[17-20] A survey study on KD during an 8-year consecutive period (January 1, 2011, to December 31, 2018) in Japan to evaluate the initial echocardiographic detection of CA lesions, Ae *et al*. found that 3.6% of patients had CA lesion.[21] Patients with delayed hospital visits were increasingly at higher risk for CA lesions detection.[21] Supplemental echocardiographic criteria for the diagnosis of incomplete KD if the CA meet JMH criteria for aneurysm are: Internal lumen diameter >3 mm in children <5 years old, or >4 mm in children >5 years old, a segment of CA measured >1.5 times that of an adjacent segment and clearly irregular coronary lumen. If echocardiographic evidence with more 3 of 6 following features: Perivascular brightness of CA, lack of tapering of CA, decreased left ventricular function, mitral regurgitation, pericardial effusion, and Z score in left or right CA of +2 to +2.5, incomplete KD can be diagnosed.[18] For the patients whose clinical manifestations are likely to KD but do not meet the diagnostic criteria, the echocardiographic findings are helpful for the early diagnosis of incomplete KD by the algorithm from AHA and the American Academy of Pediatrics.[17]

Echocardiographic Findings of Cardiac Abnormalities in Kawasaki Disease

Echocardiographic abnormalities in patients with KD include perivascular brightness of CA [Figure 1],[22] irregular lumen and wall [Figure 2], CA dilatation [Figure 3],[23] CA aneurysms [Figures 4 and 5], decreased left ventricular contractility,[24-26] mild mitral or aortic valvular regurgitation, left ventricular dilatation and pericardial effusion [Figures 6 and 7].[26] These echocardiographic findings are not only presented in typical case of KD, but can also present in the early stage of KD, which are not fulfill the diagnostic criteria of KD, and also in the patients with incomplete KD. Heuclin *et al*. reported that echocardiography was helpful in the diagnosis of 6 of 7 cases with incomplete

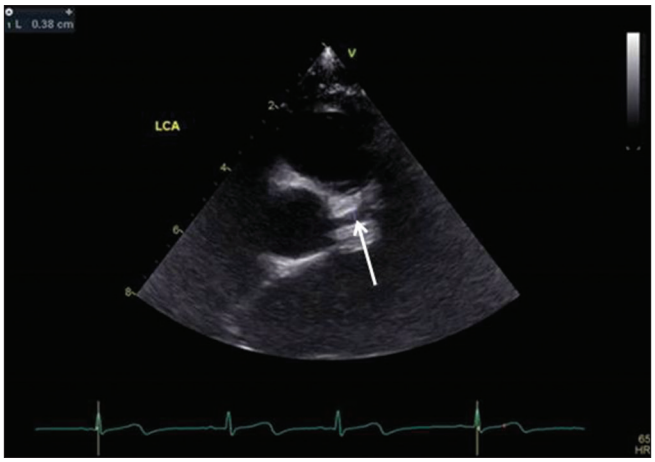

Figure 1: Parasternal short axis view of a 13 months girl is showing the perivascular brightness (arrow) of arterial wall and mild dilatation of the internal diameter as 0.38 cm of left main coronary artery on the 2nd day of high fever. LCA: left coronary artery

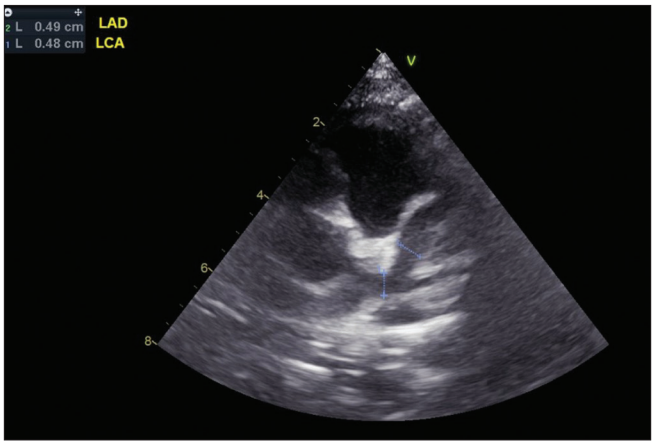

Figure 3: Parasternal short axis view is showing the diffuse dilatation of left main and anterior descending coronary arteries. The internal diameter is measured as 0.48–0.49 cm. LAD: left anterior descending artery, LCA: left coronary artery

KD. These abnormal echocardiographic findings included coronary dilatation/aneurysm, pulmonary aneurysm, mitral regurgitation, and pericardial effusion.[27,28] For the prolonged febrile infants aged younger than 6 months of age, a serial echocardiography may be an important implement as the early assistance for diagnosis of typical and incomplete KD, even the diagnostic criteria were not completely met yet.[16] To study the value of serial echocardiography in diagnosis of KD, Hörl *et al*. retrospectively analyzed 94 KD patients. They found that 24 (77.4%) of 31 incomplete KD patients confirmed the diagnosis later due to the significant increases in mean Z-scores for the left main CA, right CA, and left anterior descending arteries between the initial and second examination ($P < 0.05$).[15] So if a patient presents with clinical manifestations of suspicious KD, a serial echocardiographic evaluation may be helpful to detect the possible cardiovascular and CA changes of KD, even if the initial echocardiographic appearance and Z-score of CA were within normal range.

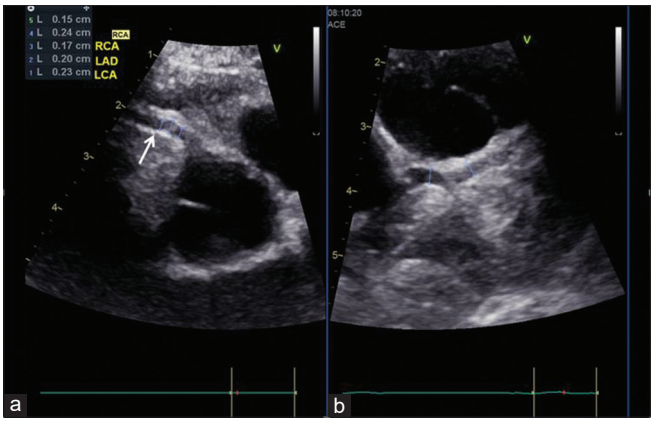

Figure 2: Parasternal short axis views of an infant with high fever for 4 days are showing the irregular lumen (arrow) of right coronary artery (a) and left main, left anterior descending arteries (b) without definitive dilatation. The internal diameter is measured as 0.17–0.24 cm. RCA: right coronary artery, LAD: left anterior descending artery, LCA: left coronary artery

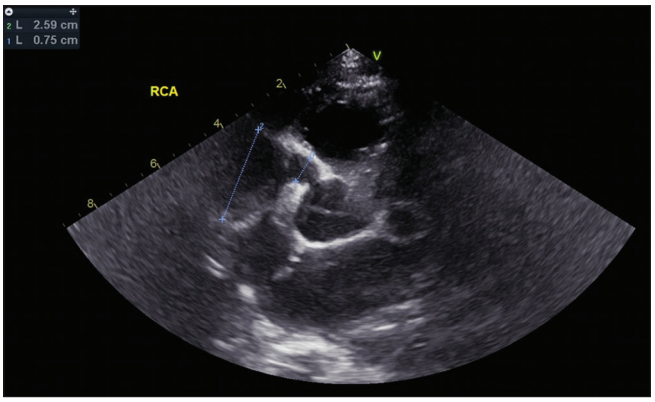

Figure 4: Parasternal short axis view is showing a giant aneurysm with internal diameter of 2.59 cm and dilatation of right main coronary artery with diameter of 0.75 cm. RCA: right coronary artery

Perivascular Brightness of Coronary Arteries

Perivascular brightness of CA has been proposed to help the early suspicious and diagnosis of typical and incomplete KD [Figure 1].[3] Rabinowitz *et al*. had a retrospective study of 117 de-identified parasternal short axis echocardiograms from 0 to 10 years of healthy, incomplete KD, typical KD, and febrile patients by 6 pediatric cardiologists interpreted blindly. They found that the absence of tapering and the presence of perivascular brightness are subjective, poorly reproducible features, and low inter-reader agreement (reliability coefficient 0.13) and can be observed in both febrile non-KD patients and healthy children.[29] Lacking of tapering and perivascular brightness are subjective, poorly reproducible features and that can be seen in febrile patients without KD and in healthy children.[29] Yu *et al*. had evaluated the significance of perivascular brightness of CA on echocardiography and concluded that those findings did not confirm as a useful diagnostic sign of incomplete KD.[22] A recent report by Azzarelli *et al*. for study the coronary external diameter index (CEDi),

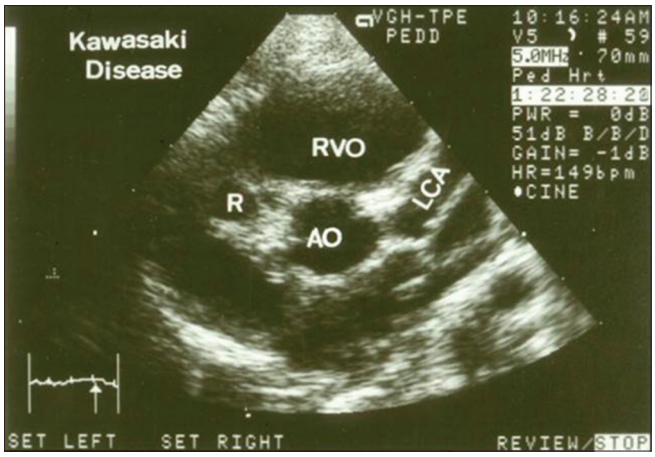

Figure 5: Parasternal short axis view is showing a fusiform aneurysm of left coronary artery and a saccular aneurysm of right coronary artery. RVO: right ventricular outflow tract, R: aneurysm of right coronary artery, AO: ascending aorta, LCA: left coronary artery aneurysm

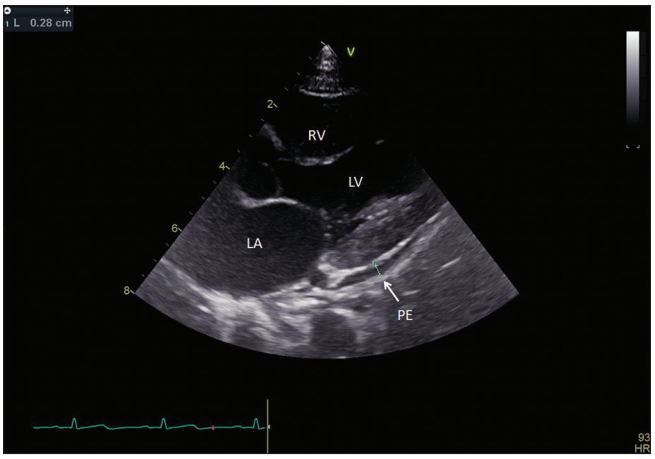

Figure 6: Parasternal long axis view is showing the echo-free space with dimension of 0.28 cm behind the left ventricular wall, indicating a small amount of pericardial effusion (arrow). RV: right ventricle, LA: left atrium, LV: Left ventricle, PE: pericardial effusion

which calculated the ratio of CA external diameter (i.e., the diameter between the outer edges of CA measured in the proximal segment of the CA) and the diameter of the aortic annulus by echocardiography in 34 patients with KD (aged 23 ± 13 months). They found that a markedly higher mean values of CEDi of both left main and right CA in KD patients than that of normal control at hospital admission ($P < 0.0001$). They also found that the mean CEDi of both right and left CA decreased significantly ($P < 0.0001$) after 2 weeks of follow-up study.[30] These findings may reflect pathologic swelling of the perivascular tissue in acute coronary arteritis, leading to increase CA wall thickness during the acute inflammatory stage of KD and manifesting as bright signals on echocardiography. Those inconsistence of the clinical significance of perivascular brightness on echocardiography for help to early diagnosis of KD were discussed and debated between many experts. In my experience and opinion, if a febrile infant without a definitive cause, the perivascular brightness of CA by echocardiography may be indicating the early signs of arteritis and a serial echocardiography daily or every other day is strongly indicated until the actual diagnosis is made.

Dilatation and Aneurysm of Coronary Arteries

During acute and subacute stage, the inflammatory CA may be presented with a range from the minimal increase in internal diameter to a giant aneurysm, which is easily accessed by the serial echocardiographic measurement.[31,32] At the beginning, the CA may present with an irregular wall and lumen [Figure 2] and then to be diffuse dilatation as ectatic or fusiform in shape [Figure 3]. The CA dilatation will evolve to be the different shapes of CA aneurysm included saccular and/or fusiform aneurysm [Figure 4]. The CA aneurysms are usually located in the epicardial CA. Many risk factors had been reported for the occurrence of the CA aneurysm.[33] There are (1) late diagnosis and delayed administration of IVIG, (2) age of onset <1 year, (3) children ≥9 years old, (4) male sex, (5) longer duration of fever more than 14 days, (6) failure to respond to initial IVIG therapy, (7) abnormal laboratory findings including low hematocrit <35%, low serum albumin, lower serum sodium, elevated alanine aminotransferase, C-reactive protein elevation, leukocytosis ≥12,000/mm^3, low baseline serum immunoglobulin G and elevation of interleukin-6 and interleukin-8.[33] The common locations of CA aneurysm are the proximal left anterior descending and proximal right CA, followed by the left main CA, circumflex CA, distal right CA, and the take-off of the posterior descending branch from the right CA.[33] The CA dilatation and/or aneurysm developed in 20%–25% of untreated KD patients and dropped significantly to about 2%–7% in patients who had been treated with high-dose of aspirin and high-dose IVIG (2 g/kg), especially the IVIG had been administrated within 10 days of onset of fever.[14,34-37] More recent reports of nationwide surveys from Japan and Korea between 2015 and 2017 demonstrated a further decrease in the incidence of coronary aneurysms to 0.82% and giant aneurysms down to 0.13%.[38] The precordial long-axis and short-axis views of echocardiography are usually to visualize and measure the diameter of the left main and right proximal CA, which were the most common location of dilatation and aneurysm.[39] The subcostal view of echocardiography to demonstrate the peripheral right coronary aneurysms was introduced by Yoshida *et al*. in 1982.[40] Satomi *et al*. reported that a systemic approach which includes short-axis aortic root plane, long-axis mitral valve plane, long-axis tricuspid valve plane, apical four-chamber plane, sagittal right atrial plane, frontal tricuspid valve plane and short axis mitral valve plane of echocardiography to visualize both the right and left CA anatomy in 1984.[41] The standard ultrasound evaluation of CA in children with KD had been reported by Fuse *et al*.[42] The definition of CA aneurysm was used to be relied on the JMH criteria in 1984.[2,18,43,44] The aneurysm or dilation of CA was defined as small aneurysm, medium, and giant aneurysm by the echocardiographic measurement of internal diameter and

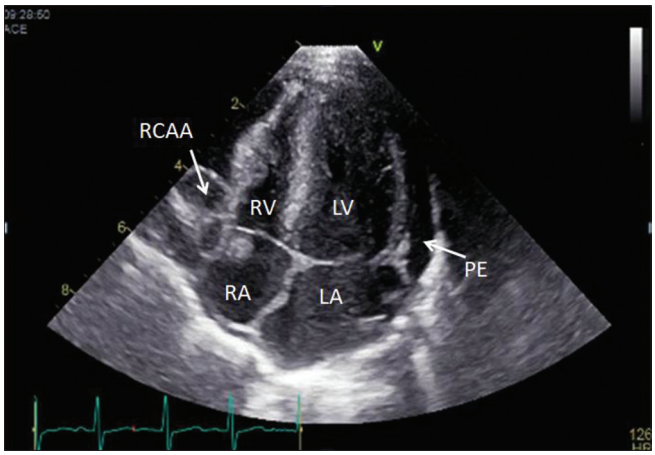

Figure 7: Apical 4-C view is showing the moderate amount of pericardial effusion around the heart (arrow) and a giant aneurysm of distal right coronary artery (arrow). RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, PE: pericardial effusion, RCAA: right coronary arterial aneurysm

compared to the internal diameter of an adjacent segment of CA.[44] Since 1998, de Zorzi *et al*. found that the prevalence of CA dilatation was significantly more common if the definition of coronary dilation was Z-score +2.5 criteria, which was obtained by using linear regression equations derived from a normal nonfebrile control population.[23] Many experts in different countries had studied their normal children and patients with KD to develop their own Z score system of CA diameter and to set the diagnostic criteria for coronary dilatation or aneurysm.[23,45-53] In 2000, AHA presented the new criteria for the definition of coronary dilatation and aneurysm with the Z score system. The CA was normal if the internal diameter <+2.5 Z-score. Small aneurysm was defined as internal diameter of CA <5 mm, medium aneurysm was defined if the internal diameter was between 5 and 8 mm, and giant aneurysm was defined if the internal diameter over 8 mm.[3] They suggested the criteria for echocardiographic abnormality in KD if: (1) left anterior descending or right CA Z score ≥+2.5, (2) CA diameter >3 mm in children <5 years or >4 mm in children ≥5 years, (3) CA lumen diameter ≥1.5 times of adjacent segment and coronary lumen is clearly irregular.[3] Many different institutes use their own different criteria for CA lesions based on the different echocardiographic findings. From the UpToDate October 2024, the CA aneurysms are defined as coronary dilation: Z-score +2 to <2.5, small aneurysm: Z-scores ≥+2.5 to <5, medium aneurysm: Z-score ≥+5–10 and absolute dimension <8 mm, larger aneurysm: Z-score ≥+10 or absolute dimension ≥8 mm.[33] Many studies found that approximately 25% of KD patients and >50% of KD infants younger than 6 months have CA aneurysm with Z-score ≥+2.5, and about 1% of them developed giant coronary aneurysm with Z-scores >±10 or absolute dimension ≥8 mm.[33] JCS Joint Working Group of Japan and AHA had established their own guideline and the definitive diagnostic criteria for KD[3,42] [Table 1]. In Taiwan, Lin *et al*. studied 412 healthy children younger than 6 years of age and set up the Formosa Z score of the diameter

Table 1: Modification of the definition of coronary artery abnormalities

Japan (Japanese Ministry of Health)
Small aneurysm or dilatation
Localized dilatation with ≤4 mm internal diameter; In children older than 5 years, internal diameter of a dilated segment, but measured <1.5 times that of an adjacent segment
Medium aneurysm
Aneurysms with an internal diameter of >4–≤8 mm; In children ≥5 years, internal diameter of a segment, measures 1.5–4 times that of an adjacent segment
Giant aneurysm
Aneurysms with an internal diameter of >8 mm; In children ≥5 years, internal diameter of a segment, measures >4 times that of an adjacent segment
USA (AHA)
Normal: *Z*-score <+2.5
Abnormal CA
Left anterior descending or right CA *Z* score ≥+2.5
CA diameter >3 mm in children <5 years
CA diameter >4 mm in children ≥5 years
CA lumen diameter ≥1.5 times of adjacent segment
CA lumen is clearly irregular
Small aneurysm: <5 mm internal diameter, or +2.5 ≤ *Z* score<+5
Medium aneurysm: 5–8, internal diameter, or +5 ≤ *Z* score <+10
Giant aneurysm: Internal diameter of >8 mm, or Z score ≥+10
Taipei VGH (my personal proposal)
Brightness or perivascular enhancement of CA
Highly suspicious (repeated echocardiography daily or every other day)
Dilatation or small fusiform aneurysm
Infant ≤2 years: Internal diameter>2.5 mm
Children >2 years: Internal diameter >3.0 mm or, +2.5 ≤Z score <+5
Medium aneurysm: Internal diameter 5–8 mm or+5 ≤ Z score <+10
Giant aneurysm: Internal diameter >8 mm or Z score ≥+10

VGH: Veterans General Hospital, CA: Coronary artery, AHA: American Heart Association

of left and right CA.[54] We adapted and modified the diagnostic criteria of JMH and AHA[2,3,18] to define the coronary aneurysm as small (+2.5 ≤ Z score <+5), medium (+5 ≤ Z score <+10), and larger (Z score ≥+10)[2,3,55] [Table 1]. If there was no initial coronary aneurysm or Z score of coronary arteries <+2 during the acute stage of KD, the CA abnormalities were very rare to be detected 1 month after the onset of illness.[56] The long-time echocardiographic follow-up studies had revealed that the fates of those dilatation or aneurysm of CA, including persistence of the dilatation/aneurysm, spontaneous regression even initial with giant aneurysm, stenosis of CA, thrombus formation to induce myocardial ischemia or infarction and sudden cardiac death.[57] The smaller the initial diameter of coronary dilatation/aneurysm was, the higher the chance to be regression of coronary dilatation/aneurysm. From an international registry study of KD, echocardiographic evidence of normalization coronary diameters were noted at 10 years in 99% of small aneurysm (+2.5 ≤ Z score ≤+5), 92% of medium aneurysm (+5 ≤ Z ≤+10) and 57% of larger (Z >+10) coronary aneurysm.[58] For the patients with larger aneurysm diameter

over 6 mm, severe stenosis or occlusion of CA with late onset of myocardial infarction were reported as higher as 5.4%.[59] Of the KD patients with persistent CA aneurysms, despite long-term use of anticoagulants, the periodic electrocardiographic and transthoracic echocardiographic examination should be the standard procedures for long-time follow-up.

Exercise Stress Echocardiography

Exercise stress echocardiography is a relatively new technique to detect regional wall motion abnormality by 2 DE.[60-63] It is the noninvasive assessment of myocardial dysfunction and has been reported as a highly sensitive and specific tool compared to other diagnostic modalities, such as single-photon emission computed tomography to identify the significant restriction in coronary blood flow.[64] It does not need to sedate children and does not expose them to radiation or contrast agents. The only possible limitation is the patient's age, which test is usually performed beyond 6 years of age. Noto *et al*. had studied 50 KD patients at the convalescent stage, and they found that the significant abnormal findings of myocardial ischemia were present in 21 of 26 patients with angiographic-proved CA disease. The sensitivity and specificity of dobutamine stress echocardiography is an accurate diagnostic method for the detection of CA stenosis in KD.[61] Tedla *et al*. found 3 of 53 (5.7%) KD patients had abnormal exercise stress echocardiograms. All the 3 patients were classified AHA Risk Level 4–5 by coronary Z-score and then were confirmed to have coronary aneurysms, stenosis, or myocardial tissue perfusion defects.[62] These findings support that the exercise stress echocardiography can be applied for the evaluation of myocardial function, including silent myocardial ischemia in KD patients with aging over 6 years despite the presence or absence of CA aneurysm by echocardiography.

Intravascular Ultrasound Study

Intravascular ultrasound imaging (IVUS) study is a new technology to assess the morphology and abnormalities of small vessels, especially for the evaluation of the CA disease with stenotic lumen, atheroma, calcification, and abnormal arterial wall during cardiac catheterization.[65] It can provide real-time tomographic imaging of vascular structures and pathological lesions in the lumen and wall of vessels.[66-68] Sugimura *et al*. studied 20 KD patients with IVUS, and they found that a markedly thickened but smooth intima at the site of a regressed coronary aneurysm and also mild intimal thickening of the echocardiographic or angiographic normal CA in KD patients. They concluded that IVUS is useful to evaluate the CA wall and for the long-term assessment of the atherosclerotic changes of CA in KD. Using virtual histology of IVUS, Watanabe *et al*. studied 18 patients with KD aged between 1 and 32 years who had CA lesions, including regressed and aneurysmal lesions. They found marked intimal proliferation and atherosclerotic changes in the CA of KD patients, not only within 1 year of onset but also in those with the disease for over 10 years.[69] Motofumi *et al*. had reported the long-term consequences of regressed coronary aneurysms after KD by IVUS study. They found that in KD patients with angiographic evidence of regressed small and larger-sized coronary aneurysms, various degrees of intimal thickening were detected. To avoid the potential risk factors of early atherosclerosis in KD patients with initial CA lesions, the IVUS may be strongly suggested. To evaluate the long-term progressive histologic/pathologic changes of CA with and without CA lesions or aneurysms in the initial stage of KD patients, IVUS during cardiac catheterization and coronary angiography may be one of the best modality to evaluate the long-term consequence of CA in patients with KD.[70-72]

Real-time Three-dimensional Echocardiography

Real-time three-dimensional echocardiography (RT-3DE) had been introduced in 1980s for clinical application to study the cardiovascular disorders, including in patients with KD.[73] It had been widely use to evaluate various abnormal cardiovascular structures, abnormalities, left ventricular thrombi, mitral stenosis, and CA for more than 20 years.[74-76] Miyashita *et al*. studied 111 KD patients with coronary aneurysms in 8, giant aneurysms in 4, and coronary dilatation in 11 by RT-3DE. CA lesions were scored as 1–4 Grades and 0–3 points. Using 2 DE and RT-3DE evaluation, they found that a significantly higher score for RT-3DE than for 2 DE ($P < 0.01$).[73] Since the complexity of the technical application and more time consumption to construct the better images, the RT-3DE was not so commonly used as 2 DE did in the clinical diagnosis and long-term evaluation of CA lesions in KD.

Ventricular Dysfunction

About 1/4 to half of patients with KD had presented with mild to moderate ventricular dysfunction, especially during the acute and subacute stages of illness. The possible causes are (1) depression of myocardial contractility by myocardial inflammation, (2) negative inotropic effects of the systemic inflammatory response, (3) ischemic cardiomyopathy due to coronary insufficiency.[33,75,76] (4) acute myocardial infarction due to thrombosis in the CA aneurysm. Echocardiographic evidence of an increase in the dimension of the left ventricle was reported in some KD patients during the acute stage.[76] Abnormal septal motion and lower left ventricular ejection fraction could be recorded. In more severe cases, pericardial effusion might be present, even with cardiac tamponade phenomenon, but it is a rare complication. In a study of 17 KD children with coronary arterial dilatation and 14 IVIG treatment-resistant children, despite the normal systolic function of the left ventricle by echocardiography, the significantly lower longitude left ventricular myocardial strain and strain rate had been recorded and might be indicating the effects of myocarditis during acute KD.[76,77] Sanchez *et al*. studied 103 KD patients at different stages, and they found a subtle decrease in strain rate of the left ventricle during the convalescent/chronic stage. These decreased effects were more pronounced in KD children with CA aneurysms which

may indicate the late decrease in myocardial function after long-term of follow-up.[78]

Cardiac Valvular Regurgitation

Since the basic pathogenesis of KD is generalized inflammatory changes, besides myocarditis, it could induce functional and pathological changes in cardiac valves, mainly the mitral and aortic valves.[78-82] Various degrees of mitral regurgitation may be caused by transient papillary muscle dysfunction, rupture of chordae tendineae, myocardial ischemia, myocardial infarction and/or dilated left ventricle due to myocarditis. Most of the valvular regurgitations are mild and will disappear gradually. All the 4 cardiac valves had been reported to be various severity of regurgitation during the different stages of KD. A nationwide surveys of 154 institutions in Japan between 2007 and 2016 reported that 290 (0.2%) KD patients presented the valvular sequelae, which including mitral regurgitation (63%), tricuspid regurgitation (39%), aortic regurgitation (13%) and pulmonary regurgitation (17%) within 1 month of KD. The incidence of mitral regurgitation, aortic regurgitation, and tricuspid regurgitation decreased significantly 1 year after KD.[79] A long-term follow-up study on 594 patients with KD, 7 (1.2%) patients presented with valvular heart disease after 10–21 years of follow-up.[83]

Pericarditis and Pericardial Effusion

Pericarditis with a significant amount of pericardial effusion is very easy to identify either by M-mode or 2 DE. An echo-free space, usually behind the left ventricular wall can be visualized either by long-axis view or four-chamber views of echocardiography. During the acute stage of KD, the presence of pericardial effusion caused by the inflammation of pericardium, myocardium, and cardiac dysfunction were reported variable ranging from 0.07% to 25%.[84-86] It is rarely to cause cardiac tamponade. Without a definitive reason, the black children with KD were reported to be more likely to have pericardial effusion.[86] The pericardial effusion usually disappeared without definitive therapy. The rare septated pericardial effusions had been reported.[87] Repeated echocardiography to detect the presence of pericardial effusion after therapy is usually needed, if the pericardial effusion has been detected during acute stage of KD.

Beyond the Heart and Coronary Arteries

The basic pathologic changes of pan-vasculitis in KD are acute necrotizing arteritis, subacute or chronic vasculitis, and luminal myofibroblastic proliferation, which results in CA dilatation, aneurysmal formation and then stenosis due to the narrowing of CA. These changes will lead to myocardial ischemia and/or infarction. Beyond the CA, these vascular changes may occur in the other arteries, such as axillary, common iliac, brachial, internal iliac, subclavain and/or carotid arteries.[33] Most of the involved arteries with an aneurysm are asymptomatic and hard to be detected unless whole-body Computed tomographic angiography (CTA), Magnetic resonance angiography (MRA) and/or Digital subtraction angiography (DSA) are performed. These high-tech medical examinations are time and money-consumption. Carotid intima-media thickness (CIMT) has been widely applied for the evaluation of structural changes of the arterial wall, which are the results of atherosclerotic changes and other inflammatory vascular diseases. It is a traditional cardiovascular risk factors of atherosclerosis, which results in cardiovascular disorder and cerebral vascular disorders.[78,88,89] A significantly greater CIMT (mean 0.55 ± 0.081 mm, range 0.44–0.69 mm) during the acute stage of KD was found to be more greater than that of the febrile children caused by other infections (0.483 mm ± 0.046 mm; range, 0.43–0.56 mm; $P = 0.01$). It suggests that CIMT could be a useful diagnostic finding in the early phase of KD.[90] However, some other reports did not find a significant difference of CIMT between KD patients and controls. Further study of CIMT in the role of evaluation of risk factors in the long-term results of vascular structural changes in patients with KD is still uncertain.[91]

Follow-up Echocardiographic Studies

Despite early and appropriate therapy, 2%–7% of children with KD still have CA sequelae after acute illness. Those CA lesions, including aneurysmal dilatation and/or stenosis are the risks for early atherosclerotic changes of CA, which may cause myocardial ischemia, angina pectoris, myocardial infarction, and sudden death. Long-term follow-up study with echocardiography is essential for those patients with CA lesions.[3,14,32,83,92] How frequency and how long to perform echocardiographic follow up are variable in different experts of different institutions.[93] In KD patients with initial CA lesions, besides the more advancing modalities such as coronary angiography, heart DSA, heart CTA, and heart MRA for CA lesions may be helpful for long-term follow-up of the CA changes, serial echocardiographic studies are noninvasive and easy to perform even in uncooperative infants and toddlers. The latest Japanese guidelines for the management of cardiovascular sequelae have recommended to do follow-up echocardiographic studies at least 5 years for patients with normal or transient dilatation of CA.[94] Since new CA arterial abnormalities occurring after 1 month of KD are rare, some experts had suggested that follow-up echocardiography beyond 2 months may not be warranted in patients without CA lesion during the acute stage of illness. On the contrary, occult dilation of CA with echocardiographic evidence of reductions in size over time of initially grouped as normal CA has been reported as higher as 27% in a study of 129 patients with KD.[95] Besides that, the peak rates of emptying of the left ventricle and thickening of the posterior wall of the left ventricle were significantly reduced in 67 KD patients without demonstrable CA disease, even 12 months after the onset of KD.[96] In our institution, for the KD patients without initial CA lesions, we will treat the patients with 3–5 mg/kg/day of aspirin and undergo electrocardiogram recording and echocardiographic evaluation 1 week after discharge, and then 1 month and 3 months later. If they are

asymptomatic and have negative findings on electrocardiograms and echocardiograms, they will be discontinued to take aspirin and will receive electrocardiography and echocardiographic evaluation again 6 months later, and then once a year for 5 years. After that, a Treadmill test for rule out of possible myocardial ischemia during exercise will be performed during the entering to primary school. If there is dilatation/aneurysm of CA persistent, they will be keeping on Aspirin therapy and also have electrocardiograms and echocardiographic evaluation every 3–6 months. If there is a giant aneurysm of CA, Persantin or Warfarin will be added. If there are any symptoms or signs of myocardial ischemia occurring during the follow-up period, further studies such as Holter's monitor recording, CTA, MRA, and cardiac catheterization with coronary angiography will be considered. Artificial intelligence with deep learning techniques is a newly development in the medical field to assist in diagnosis for view classification and object detection by cardiac ultrasound.[97] Kuo *et al*. had proposed a framework named Scaled-YOLOv4-HarDNet to detect the dilatation and brightness of CA, which may aid in early detection in possible KD patients and may make an early decision of special treatment.[98]

Summary

KD is an important systemic vasculitis in childhood. The complications of this particular disorder may result in CA lesions, including aneurysmal dilatation and stenosis, and then finally lead to early onset of CA disease, myocardial ischemia, acute myocardial infarction, and even sudden cardiac death in childhood and young adulthood. Besides the clinical presentations, Electrocardiography, and other laboratory tests, echocardiography is still the basic diagnostic tool to detect the CA lesions and the structural and functional changes of the cardiovascular system during acute, subacute, and convalescent stages of illness. It can also be useful for long-term follow-up studies of the cardiovascular structural and functional changes, including the valvular changes and CA sequelae. If there are no definitive echocardiographic abnormalities during the initial 3 months of illness, treatment and repeated echocardiographic study may not be necessary. However, if there are any CA abnormalities, including irregularity, dilatation/aneurysm, and cardiac valvular changes, long-term management and echocardiographic follow-up studies are necessary. Other diagnostic modalities, including ECG, Holter's monitor recording, nuclear medicine study of myocardial ischemia, cardiac catheterization, coronary angiography, heart CTA, and MRA may be needed depending on the clinical presentations of myocardial ischemia in individual patients with KD.

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Conflicts of interest

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