My approach to assess Kawasaki disease by echocardiogram

Como Eu Faço Diagnóstico e Avaliação Ecocardiográfica na Doença de Kawasaki

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Abstract

Kawasaki disease is the leading cause of acquired disease in children worldwide. The varied spectrum of this disease makes it both interesting and challenging to diagnose and follow up.

Kawasaki disease (KD) is an acute and self-limited disease of unknown etiology. A medium-sized artery vasculitis, it affects mainly the coronary arteries in approximately 25% of untreated patients and around 4–5% of those treated with intravenous immunoglobulin (IGVI) with the consequent formation of coronary artery aneurysms.[1,2] Other arteries can be affected, such as the subclavian, brachial, axillary, iliac, and femoral arteries, and occasionally the renal arteries and abdominal aorta.

The diagnosis of the disease remains eminently clinical and follows the classic criteria established by the American Heart Association,[3] according to which fever should persist for at least 5 days and be associated with four of the signs listed in Chart 1. Certainly, there are peculiar situations in which patients with fever for > 5 days and who demonstrate fewer than four other clinical signs already have coronary involvement on echocardiography, confirming the early KD diagnosis. More than the four main criteria may be evident before the fifth day of fever, leading to an early diagnosis of the disease and enabling earlier treatment.

KD mainly affects children up to 5 years of age, with a peak incidence between 9 and 11 months of age.[1] Although the disease is rare in babies up to 3 months of age, some cases have been reported.[4] Ischemic cardiac lesions, such as an undiagnosed KD sequela in childhood, correspond to 5% of acute coronary syndrome cases in adults aged < 40 years.[5] The varied spectrum of this disease makes it very interesting and challenging to diagnose and follow up.

Keywords

Coronary Aneurysm; COVID-19; Echocardiography; Kawasaki disease.

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Manuscript received 5/7/2020; revised 5/21/2020; accepted 5/27/2020

DOI: 10.47593/2675-312X/20203304eabc106

Because specific diagnostic tests for KD are lacking, clinical recognition is of great importance for the therapeutic management of these patients, as a delayed or misdiagnosis can compromise the disease course and patient prognosis. Thus, echocardiography is extremely useful and valuable in cases of KD.

The echocardiographic study in KD focuses on the coronary arteries, which are affected by its major sequelae. Echocardiography is the imaging method of choice in cardiac evaluation due to its high specificity and sensitivity for detecting coronary artery abnormalities and noninvasive nature. It should be performed as soon as the diagnosis is suspected with the aim of visualizing all coronary segments. Echocardiography is a great tool even in cases of incomplete KD, which are characterized by the presence of fever for > 5 days but fewer than four of the associated clinical criteria listed in Table 1. In these cases, the finding of echocardiographic changes enables the diagnostic conclusion of the disease, greatly assisting with its clinical management (Table 2).[6]

The coronary artery should be measured between the internal extremities of the vessel on two-dimensional echocardiography in several planes, excluding the coronary ostia and branching points, in which the focal dilation is normal. In addition, perivascular brightness and echogenicity, which tend to increase in KD, and wall and flow irregularities on Doppler and color mapping should be observed.[7]

Several methods for analyzing coronary artery dimension have been reported. The dimension indexed by body surface

Table 1 - Diagnostic criteria for Kawasaki disease.

Fever for at least 5 days
Four of the following signs:
Bilateral conjunctival hyperemia
Changes in the oral mucosa:
Erythema or cleft lip
Diffuse or oropharyngeal erythema
Raspberry tongue
Extremity changes:
Hardened hand and foot edema
Palmoplantar erythema
Desquamation, usually periungual
Polymorphous rash
Cervical adenomegaly (>1.5 cm in diameter)

Note: Kawasaki disease can be diagnosed before the fifth day of disease in cases of fever and four of the other signs.

Editorial

(Z score) provides a more objective and accurate value, being the most valid score in the diagnostic and prognostic evaluation of these patients (Figure 1). Z score ≥ +2.5 is considered abnormal. Dallaire and Dahdah published the Z score calculation of the coronary arteries in all segments based on expected body surface values at all ages, increasing the importance of these echocardiographic measures.[8] The Z score can be quickly and effectively calculated at www.parameterz.com. Kobayashi et al. created a ready-to-use Z score calculator based on Microsoft Excel software to facilitate the specialists' routine (http://raise.umin.jp/zsp/calculator/). The calculator provides a median coronary artery diameter (Z score = 0) and the ratio, that is, the determined value divided by the median.[9]

Left coronary dilation usually does not involve the ostium and rarely occurs without ectasia of the anterior descendant and/or the circumflex arteries. Ectasia or coronary dilations are considered when the Z score is 2–2.5. At values > 2.5, they are already considered aneurysms. They are considered saccular when the axial and lateral diameters are approximately equal and fusiform if the dilation is symmetrical with proximal and distal thinning.[10] The number and location of aneurysms and the presence or absence of thrombi should also be investigated (Figure 2, Video 1). Table 3 clearly summarizes the classification of echocardiographic coronary changes according to the Z score, which must be followed by every echocardiographer.[10]

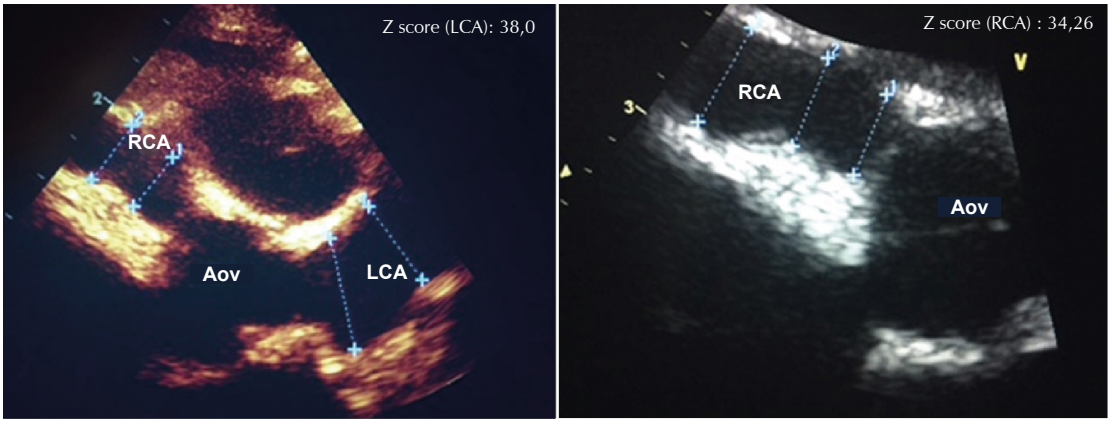
Table 2 - Conditions that confirm the suspected diagnosis of Kawasaki disease on echocardiography.

Z score of the right coronary or anterior descending artery internal diameter ≥ +2.5 or coronary aneurysm
OR at least three of the following findings:
Pericardial effusion
Mitral valve regurgitation
Left ventricular systolic dysfunction
+2 < coronary Z score < +2.5
↑ perivascular brightness and loss of usual coronary thinning

The aortic root should also be measured and compared with reference body surface values because there is evidence of mild aortic root dilation being common in patients with KD.[11] The pericardium and valves should always be evaluated with respective analysis of pericardial thickening and/or effusion and the presence and quantification of valve regurgitation as well as the anatomical characteristics of the valves, mainly the mitral and aortic.

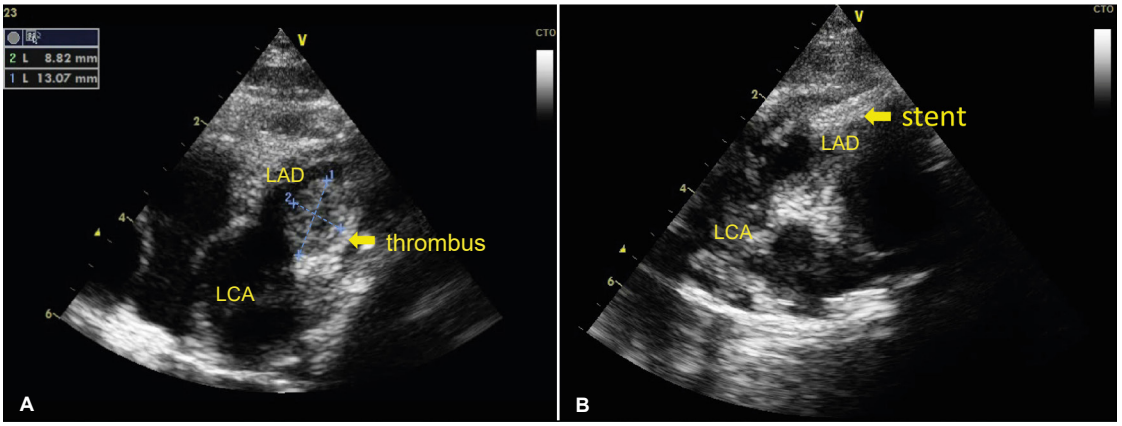
Myocarditis in the acute phase is common in histological studies. Thus, the evaluation of left ventricular function is necessary in all patients with KD. Left ventricular performance can be evaluated using one-dimensional ejection fraction by calculating diastolic and systolic volumes from the left ventricle to two- and three-dimensional flows, dP/dT measured in a mitral regurgitation jet when present, and the myocardial performance index or Tei index.[10] The evaluation of myocardial deformation by strain using speckle tracking favors the direct analysis of the movement of myocardial fibers in different directions, making it a valuable tool for the early detection of systolic and diastolic dysfunction and segmental contractility changes and a promising technique for the diagnosis and follow-up of patients with KD[12] (Figure 3). It is worth mentioning that the American Heart Association has already incorporated the use of echocardiographic evidence of ventricular dysfunction as auxiliary criterion for incomplete Kawasaki diagnosis.[10] In the diagnostic phase it can be a more sensitive indicator of myocardial inflammation. McCandles et al.[13] demonstrated a reduction in LV GLS and strain rate to the initial echocardiogram of patients with KD who later came to develop coronary dilation, or although they showed resistance to the treatment with IGVI. The patients who did not develop coronary dilation and who responded promptly to treatment, had GLS LV and strain rate comparable to that of the healthy control group on the initial echocardiogram. These findings suggest that the strain LV should be used as a stratification tool for risk at Kawasaki disease.[13]

Follow-up echocardiography should be performed at the time of suspected diagnosis, 2 weeks thereafter, and between 6 to 8 weeks after disease onset in uncomplicated



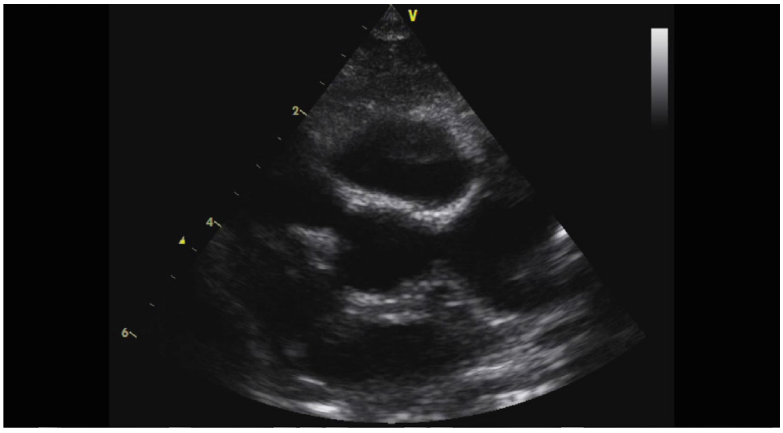
RCA, right coronary artery; Aov, aortic valve; LCA, left coronary artery.

Figure 1 – *Transthoracic echocardiogram taken in the transverse short-axis plane showing the giant right and left coronary aneurysms and the respective Z scores in an infant with Kawasaki disease diagnosed at six months of age.*



left anterior descending artery (LAD); left coronary artery (LCA).

Figure 2 – *Transthoracic echocardiogram showing the evolution of the infant in figure 1. (A) Eleven months after Kawasaki's disease, thrombus in the left coronary artery (LCA) and in the left anterior descending artery (LAD) in the short axis parasternal plane. (B) Two-dimensional echocardiogram shows stent implanted in LAD after acute myocardial infarction and cardiogenic shock.*



VIdeo 1 – *Infant with coronary aneurysms in the right, left and anterior descending coronary artery (LAD) evolved with thrombus, acute myocardial infarction and shock due to LAD obstruction. Stent was successfully implanted. The video shows the evolution of the case through echocardiographic study from the diagnosis of aneurysms, thrombus formation, obstruction of LAD on color mapping and post-stent evaluation.*

Table 3 - Classification of coronary changes on echocardiography by Z score.

No changes: Z score < 2
Dilatation only (ectasia): Z score of 2–2.5; or if initially <2 with an increase of ≥1 that occurs during follow-up
Small aneurysm: Z score ≥ 2.5 to <5
Medium aneurysm: Z score ≥ 5 to <10
Large or giant aneurysm: Z score ≥ 10 or absolute value ≥ 8 mm

cases. More frequent echocardiographic evaluations may be necessary in high-risk children with persistent fever, coronary abnormalities, ventricular dysfunction, pericardial effusion, or valve regurgitation. Additional echocardiographic studies after 8 weeks are not recommended in patients with previous normal findings due to the improbability of changes,[14] although this approach is not universally adopted due to interest in the long-term evaluation of the coronary flow reserve and dilation of the aortic root in previously normal patients. The need for longitudinal follow-up was reinforced by Crystal et al., whose study showed that > 50% of patients with a coronary artery Z score initially within the normal range showed a decrease in follow-up evaluations with greater detection of coronary abnormalities on subsequent echocardiograms.[15] Therefore, patients with slight or moderate coronary dilation should undergo an echocardiographic evaluation annually, while those with significant coronary dilation or obstruction should undergo the examination every 6 months (Tabela 4).[10]

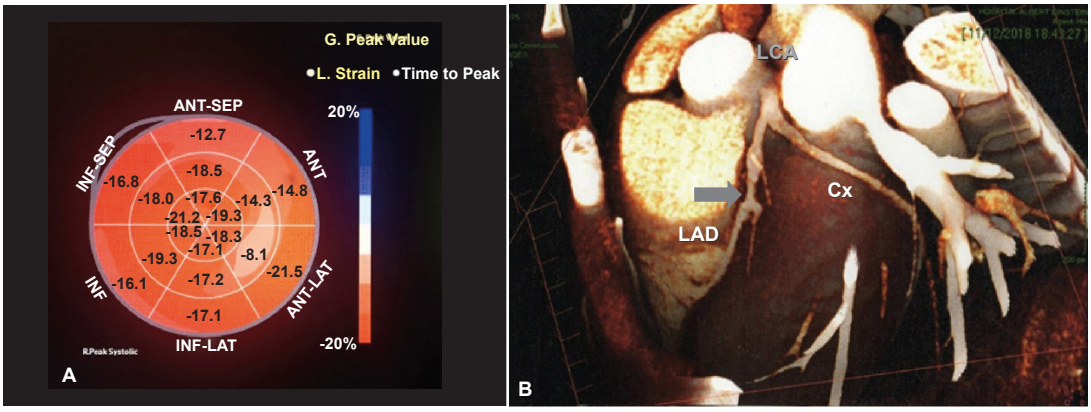
The echocardiogram has some limitations, as in the evaluation of distal coronary segments and in the follow-up of patients with KD regarding adequate visualization of the coronary arteries, which can become progressively more difficult as children grow. Thus, the use of other diagnostic modalities may become

necessary, such as transesophageal echocardiography (Video 2), especially in rare cases of surgical myocardial revascularization and, more often, on coronary computed tomography angiography, when documenting improved detail of coronary lesions, aneurysms, stenoses, and thrombi becomes necessary.

The delayed or misdiagnosis of KD increases the likelihood of coronary artery lesions. Coronary aneurysms or moderate coronary dilation may persist or remodel.[16] Left ventricular systolic dysfunction tends to normalize during the subacute phase of the disease.

Stenotic coronary artery lesions are generally progressive due to myointimal proliferation and can lead to ischemia and death years after KD.[17] Patients with KD require monitoring and stratification by the relative risk of developing myocardial ischemia using functional tests,[18] which should be complemented by further tests depending on the magnitude of the identified coronary lesions (Table 4). Myocardial perfusion evaluation tests, such as stress echocardiography, myocardial scintigraphy, and magnetic resonance imaging with myocardial viability, must be critically performed in patients with coronary aneurysms. Angiography with intracoronary ultrasound, fractional flow reserve (FFR) and optical coherence tomography (OCT) are indicated in the most complex cases to evaluate therapeutic programming.[19]

Several studies suggested that genetic influences on the magnitude and nature of the immune response may determine KD susceptibility.[18] Conventional methods failed to discover the causative agent; without this information, specific



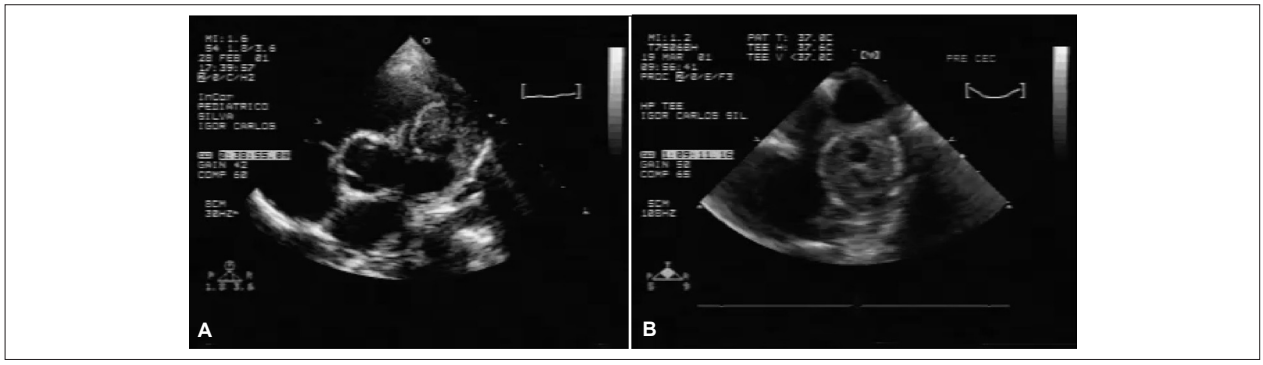
LAD, left anterior descending; LCA, left coronary artery; CX, circunflex.

Figure 3 – *Echocardiographic speckle tracking study in a 15-year-old adolescent who presented with Kawasaki disease at 2 years of age and had a 90% right coronary obstruction who successfully underwent drug-eluting stent placement. The evaluation of longitudinal deformation by strain performed 6 months after the hemodynamic procedure showed decreased values in the anterior wall. Computed tomography angiography performed later detected 50% obstruction of the left anterior descending artery.*

Table 4 - Guidance on sequential follow-up cardiovascular examinations in patients after Kawasaki disease by risk level.

Risk level	Follow-up and diagnostic examination	Invasive examination
I (without coronary artery changes at any disease stage)	Cardiovascular risk evaluation at 5-year intervals	Not recommended
II (transient coronary artery ectasia disappears within the first 6–8 weeks)	Cardiovascular risk evaluation at 3- to 5-year intervals	Not recommended
III (small to medium coronary artery/main coronary artery aneurysm)	*Annual cardiological follow-up with echocardiography + EKG combined with cardiovascular risk evaluation; biannual myocardial perfusion test/stress test*	Angiography if noninvasive test findings are suggestive of ischemia
IV (1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in the same coronary artery without obstruction)	*Biannual cardiological follow-up with echocardiogram + EKG; annual myocardial perfusion test/stress test*	First angiography at ≤ 6–12 months if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings are suggestive of ischemia; repeated elective angiography in some circumstances
V (coronary artery obstruction)	*Biannual cardiological follow-up with echocardiogram + EKG; annual myocardial perfusion test/stress test*	Recommended angiography to approach therapeutic options

EKG, electrocardiography.



Video 2 – *(A) Transthoracic echocardiogram of a 7-year-old child with a history of Kawasaki disease progressing with chest pain showing a giant aneurysm and a thrombus occluding the left anterior descending artery. (B) Transesophageal echocardiogram taken during myocardial revascularization confirming the previous findings.*

diagnostic tests, preventive measures, and treatment for KD cannot be developed.

Many immunological changes occur in KD, such as cytokine cascade stimulation (interleukin 1, interleukin 6, tumor necrosis factor, and gamma interferon) and endothelial cell activation. Although the real mechanism that causes arteritis is not well understood, the activation of endothelial cells, CD68+ monocytes/macrophages, CD8+ lymphocytes, and oligoclonal immunoglobulin appear to be involved. The prominence of immunoglobulin A in the respiratory tract suggests the airway as a gateway for disease-triggering agents.

Recently, with the severe acute respiratory syndrome coronavirus 2 pandemic, many children and adolescents worldwide have presented a clinical status similar to that of KD and a multisystemic inflammatory syndrome characterized by a cytokine storm. It is speculated that this condition may be associated with a later immune reaction to the virus (by about 6 weeks). The cardiac involvement in these patients presents as pancarditis with possible myopericarditis, pericardial effusion, and mitral valve regurgitation. Echocardiography shows increased echogenicity of the interventricular septum, atrioventricular junction, and crux cordis in addition to coronary artery involvement with increased brightness and perivascular refringence and sometimes, dilations, and aneurysms. A peculiar aspect associated with patients with KD and coronavirus disease 2019 is that myocarditis with myocardial dysfunction seems to be even more severe and appear in older age groups, possibly affecting older children and adolescents.[20,21] Kawasaki-like usually presents greater hemodynamic instability and severity. The treatment also consists of IGIV and AAS, sometimes being necessary the use of corticosteroids, low molecular weight heparin and even immunomodulators such as interleukin-1 inhibitor (Anakinra) and interleukin-6 inhibitor (Tocilizumab), in refractory cases.[22,23] Institutions from around the world, including Brazil, are collaborating to study and advance the diagnostics, preventive approaches, and therapies for these diseases, and much work has yet to be done.

Conflict of interest

The author have declared that they have no conflict of interest.

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