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REVIEW ARTICLE — DISEASE DISCOVERED IN JAPAN AND THE ROLE OF NUCLEAR CARDIOLOGY

Current Status of Kawasaki Disease and the Role of Nuclear Cardiology

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Abstract

Kawasaki disease (KD) has become a commonly acquired heart disease worldwide in children over the past five decades, because of the related cardiac sequelae. KD is an acute generalized medium vasculitis resulting from hypercytokinemia, and the coronary artery lesions caused by KD from childhood to adulthood lead to ischemic heart disease. To treat and manage KD appropriately, the optimal use of nuclear imaging is required.
Keywords: Coronary artery aneurysm, Coronary revascularization, Extent score, Kawasaki disease, Myocardial ischemia, Myocardial perfusion imaging
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Kawasaki disease (KD) is an acute febrile vasculitis of an unknown origin, often found in children under 5 years old. It was first reported by Dr. Tomisaku Kawasaki in 1967 (1). Although KD had been considered “a benign disease,” the first national KD survey at 1970 in Japan indicated 1.4% of cardiac deaths due to coronary artery involvement (2). KD has become a commonly acquired heart disease worldwide in children over the past five decades, and the highest disease prevalence is found in Japan. Post-KD patients with coronary sequelae over time from childhood to adulthood develop ischemic heart disease. There are undoubtedly some asymptomatic adult patients with coronary artery lesions (CALs) caused by KD who remain undiagnosed, although the number of patients with acute coronary syndrome due to KD-related CALs is very small (3, 4).

Acute KD vasculitis and cardiac sequelae

Acute KD vasculitis is a hypercytokinemia involving general medium-sized vessels. The occurrence of this disease depends on abnormal immunologic responses and on hereditary factors. Recently, some susceptible genes related to activated T-cells have been identified (5). Acute KD vasculitis is a self-limiting disease subsiding within two weeks in most patients (1), and has six major principal symptoms: 1) fever persisting for ≥5 days; 2) bilateral conjunctival congestion; 3) changes in the lips and oral cavity; 4) polymorphous exanthema; 5) changes to the peripheral extremities; and 6) acute non-purulent cervical lymphadenopathy. However, some patients have a recrudescent fever with recurring relapses and symptoms that are widespread throughout the body; the diffuse nature of the disease may lead the physician to making an incorrect diagnosis. Further, KD may be associated with coronary artery aneurysms (CAAs) in about 20% of the patients without appropriate treatment (6).

Standard therapy for acute KD involves high-dose intravenous immunoglobulin (IVIG) (2 g/kg/day) with aspirin (7). However, one fifth of IVIG recipients have a persistent or recrudescent fever, and additional IVIGs are needed in these cases. Some patients require further adjunctive therapies; resistant cases may receive corticosteroids, cyclosporine, tumor necrosis factor-alpha blockers, and plasmapheresis (8). However, there is no current therapy guaranteed to be effective, and the above drugs are often used in combination.

Pathologically, coronary arteritis begins at 6 to 8 days after the onset of KD, resulting in neutrophils and lymphocytes infiltrating into the arterial wall from the media and adventitia (2). When the structural components of the arterial wall are damaged, arterial dilation occurs (~12 days after the onset of

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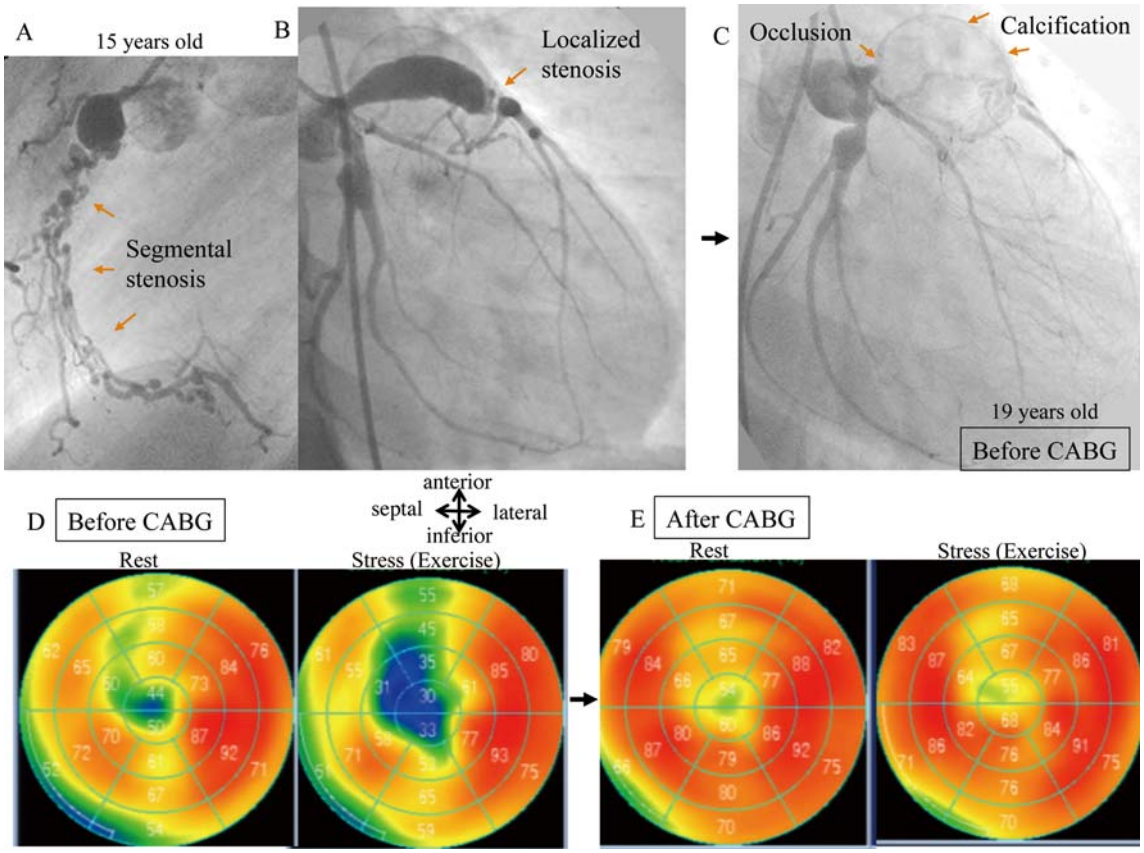


Figure 1 Selective coronary angiograms and myocardial perfusion imaging (MPI). This male patient had KD at the age of 2 years old. He underwent coronary artery bypass grafting (CABG) to the left anterior descending artery (LAD) and the posterior descending artery of the right coronary artery at 19 years old, because of myocardial ischemia.

A: Right coronary angiogram at 15 years old showing a segmental stenosis and aneurysm. Segmental stenosis means small, new vessels after a thrombotic occlusion in the aneurysm.

B: Left coronary angiogram at 15 years old indicating a giant aneurysm with calcification and localized stenosis of the LAD.

C: Left coronary angiogram at 19 years old showing an asymptomatic occlusion of the LAD.

D: Myocardial hypoperfusion in the anteroseptal wall of the left ventricle during an exercise stress test was detected in the MPI at 19 years old (before CABG). SRS 14, SSS 26, SDS 9, Extent score (rest) 23, LVEF* rest 53%, exercise 46%.

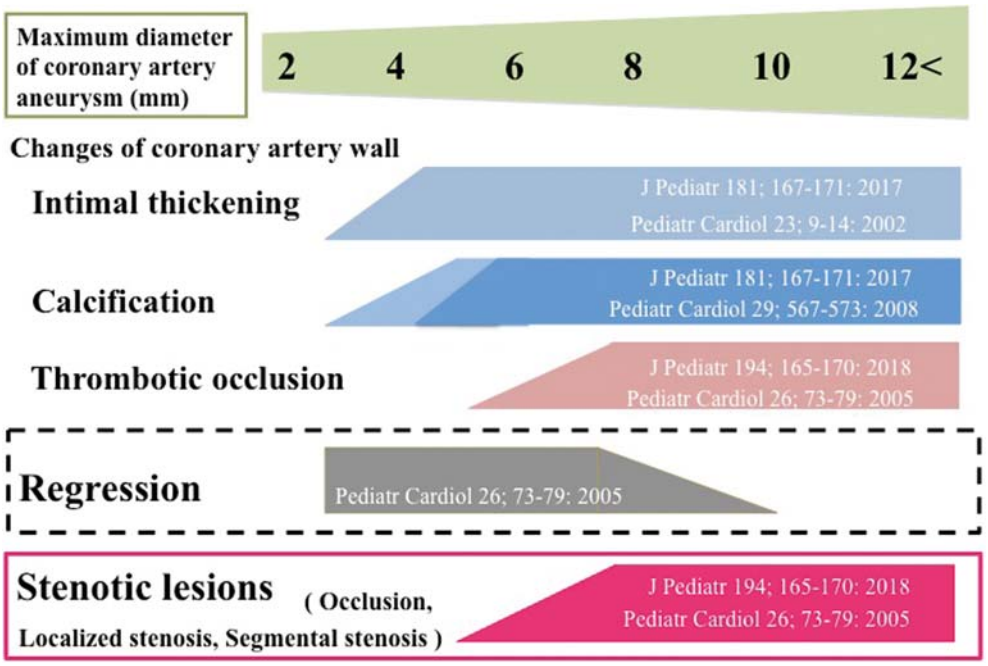
E: After CABG, the myocardial hypoperfusion in the MPI improved. SRS 5, SSS 6, SDS 1, Extent score (rest) 17, LVEF rest 58%, exercise 60%. * left ventricular ejection fraction.

KD). Therefore, the goal is to alleviate the fever within 10 days of illness. We believe that the optimal time for the initial IVIG is five to seven days after the onset of KD, because a recurrent and persisting fever can be the cause of CAAs. In Japan, the annual number of KD patients has increased to approximately 15,000 people. The proportion of patients with CAAs in the acute phase is 5.6%, and one month after KD onset it is 1.3%. Further, giant aneurysms exceeding 8 mm account for only 0.13% of the patients, and giant aneurysms are three times more prevalent in males.

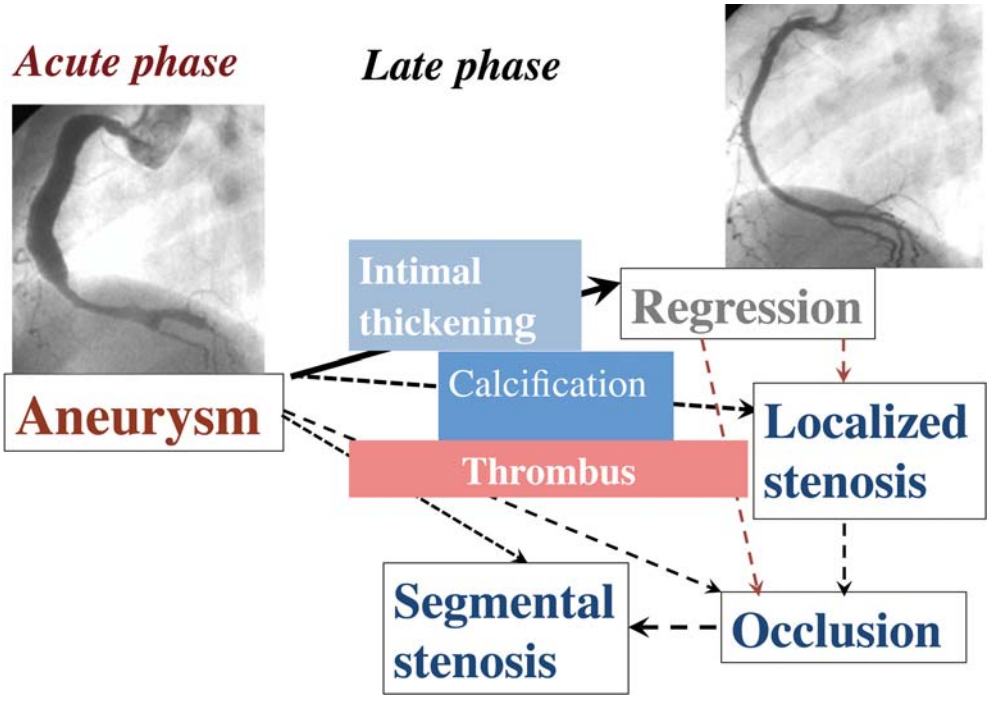
Characteristics of CALs caused by KD

The following characteristics are commonly observed in KD-related CALs. First, a giant aneurysm is commonly found in the proximal portion of the major coronary arteries (Figure 1A and B). Second, thrombotic occlusion and segmental stenosis such as “braid-like appearance” are likely to occur in the first year of acute KD (Figure 1A) (9, 10). Third, a progressive coronary wall that thickens over time with calcification exists (Figure 1B, 1C) (11). Fourth, asymptomatic occlusion due to developed collateral arteries is present (Figure 1C). These morphologic changes of the coronary arteries in the late period depend on the degree of injury due to acute vasculitis to the coronary artery wall. The initial maximal diameter of the CAAs, <100 days after the onset of KD in the selective coronary angiograms (CAGs), reflects on the extent of injury in the coronary artery wall during the acute phase, and can be used as a marker to predict morphologic changes in the late period (Figure 2A, 2B) (10).

Regression of CAAs in the CAGs of the late period refers to “apparently angiographical normal coronary arteries” (Figure 2A and B). It does not necessarily indicate “normal coronary arteries”. Regression often leads to complete coronary occlusion, which occurs in acute coronary syndrome. Late,



(A)



(B)

Figure 2

A: Maximum diameter of the coronary artery aneurysm in the selective coronary angiograms within 100 days of the onset of KD and the morphological change in the late period.
Stenotic lesions include localized stenosis, segmental stenosis, and complete occlusion.

B: Various morphological changes of the coronary artery aneurysms in the late period.

severe, localized stenosis due to intimal thickening of the vessel walls, reflecting myofibroblastic proliferation, may eventually be completely occlusive and lead to myocardial ischemia. The time of the appearance of localized stenosis varies, ranging from several months to more than 10 years after the acute KD episode in a given patient. Giant aneurysms (>8 mm) are likely to occlude the vessel with thrombosis, especially during the first year, which often leads to acute myocardial infarction (Figure 2A and B). Acute myocardial infarction can occasionally cause sudden death or impair left ventricular function. Myocardial involvement due to myocardial infarction in childhood can lead to late sudden death in adults, becoming a major determinant of outcomes for this population (12).

Role of imaging in patients with CALs caused by KD

Recognition of CALs caused by KD depends on the imaging technique. The detection of CAAs and the cardiac function by two-dimensional echocardiography is both convenient and repeatable at the bedside in the acute phase. While the gold standard technique for coronary artery imaging is selective coronary angiography, the management of CALs is greatly assisted by the application of non-invasive methods such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), and nuclear imaging. Additionally, the diagnosis of CALs and measurement of the coronary arteries by CTA and MRA have been shown to be reliable. The diagnostic accuracy of CTA comparing with CAG was excellent (k=0.93) (13). Over the past four decades in this population of patients, nuclear imaging has also been performed as an acceptable imaging modality to evaluate myocardial involvement (14).

Usefulness of nuclear imaging

Myocardial perfusion imaging (MPI) by quantitative gated single photon emission computed tomography (SPECT) has two major roles, when evaluating the myocardial involvement caused by CALs due to KD. One is the detection of myocardial ischemia, and the other is assessing for the existence of irreversible myocardial damage (15). Therefore, the evaluation of the myocardial viability by MPI has become a prominent tool for decision of coronary revascularization, in combination with stress testing results (Figure 1D) (16). MPI has also been used as a non-invasive evaluation method in children. Total and regional myocardial blood flow measured by ^{13}N-NH_3 PET positron emission tomography (PET) is the gold standard for evaluating myocardial viability, and is possible in patients with multi-vessel coronary artery disease (17, 18). Although hybrid cardiac imaging such as SPECT/CT and PET/CT are useful, radiation exposure by the examinations should be minimized in children (14). The detection of vascular inflammation in adults with the history of KD was reported by ^{18}F-fluorodeoxyglucose-PET/CT (19).

The radionuclear tracer of ^{201}Tl in the past and ^{99m}Tc currently have been used. The use of ^{99m}Tc-tracer has improved the quality of imaging and the reduced exposure to radiation. Pharmacological and exercise stress imaging are common methods of stress-induced myocardial ischemia, and pharmacological stress MPI is often performed in small children with dipyridamole (0. 56 mg/kg/4 min) (15). Adenosine and dobutamine are also used (14, 16, 20). In exercise stress MPI, the ergometer is often used in school-aged patients (21).

Recently, the assessment of the various parameters by MPI has been used to predict future cardiac events in patients with coronary artery disease. Cardiac events are based on myocardial defects during stress testing and on the left ventricular ejection fraction. The following parameters of myocardial perfusion defects used are: summed rest score (SRS); summed stress score (SSS); summed difference score (SDS); and extent score. Further, multivariate risk models including age and other variables have developed. The extent of myocardial hypoperfusion in patients with CALs after KD is significantly related to the appearance of non-sustained ventricular tachycardia in the late period (22). The following describes the extent score: short axis images of the left ventricle were obtained after reconstruction, then, in each short axis image the ischemic lesions were analyzed in the circumferential area. Hypoperfusion <2 standard deviation from the mean was defined as an ischemic lesion, and its area was the extent of hypoperfusion. Summation of the extent from the apical layer to the basal layer was defined as the extent score. Extent scores were automatically calculated by Quantitative Perfusion SPECT (QPS) software developed by the Cedars-Sinai Medical Center. Adolescence and young adults with extent score ≥11% have a risk of fatal ventricular arrhythmia (12, 22).

Conclusion

MPI is a non-invasive and acceptable modality for the evaluation of myocardial viability and cardiac function. Additionally, findings on nuclear imaging are useful in the decision for coronary revascularization surgery and in prediction of the future events in patients with multi-vessel disease caused by KD.

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Conflicts of interest

None.

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