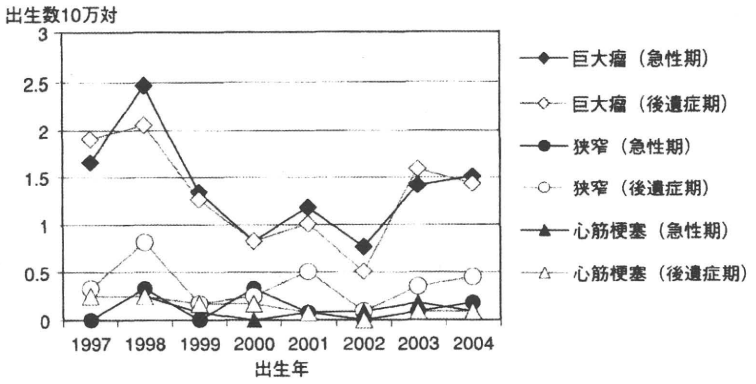

図6　急性期と後遺症期の巨大瘤，狭窄，心筋梗塞，累積罹患率（3歳時）
3歳時での冠動脈巨大瘤病変と狭窄病変，さらに心筋梗塞の累積罹患率について，出生年別の推移を急性期と後遺症期を対比して表している。

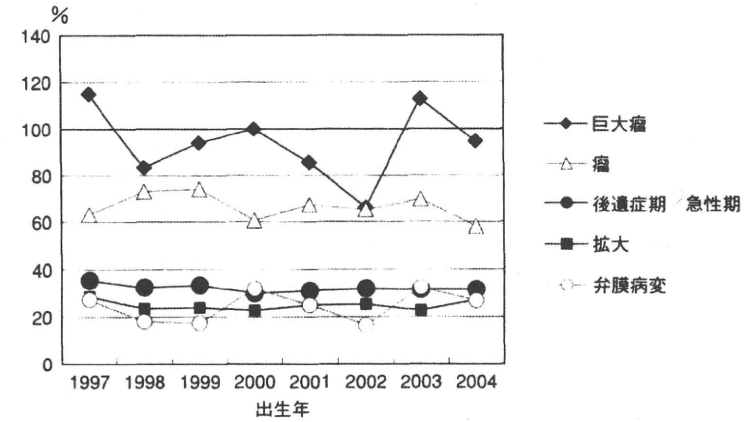

図7　急性期病変から後遺症期病変への遺残率　巨大瘤，瘤，拡大，弁膜病変（3歳時）
3歳時での冠動脈の巨大瘤，瘤，拡大病変および弁膜病変において，後遺症期累積罹患率を急性期累積罹患率で除し，100分率で表した遺残率についての出生年別推移をみている。

障害後遺症期累積罹患率を心障害急性期累積罹患率で除した値である約30％ぐらいを平均とすると，巨大瘤，瘤病変はそれにくらべて高く，瘤は60％以上残存するようであった。巨大瘤は100％を越すコホートがあった。

Ⅳ．考　　察

1970年に川崎病研究班が発足して以来，多数の小児科医の協力を得て2006年までに19回の全国調査がなされている。そのデータについては，種々の研究者からのデータ提供要請に対し，目的を確認し，必要な情報しか提供しないなどの個人情報の守秘管理に十分に配慮しつつ提供されている[5]。それらのデータをもとに，川崎病の出生年コホート別川崎病累積罹患率について，われわれは過去に報告している[6]。出生年コホート別川崎病累積罹患率は，1977年1月から1995年12月までに生まれた患児を対象に，10歳時の累積罹患率を分析したもので，年間川崎病罹患率のグラフの変動を1年前にずらすと，累積罹患率の変動の傾向は一致し，1986～1995年コホートまで毎年上昇していると報告した。

また，心後遺症についても，1983年1月から2002年12月までに生まれた患児を対象に，10歳時の出生年コホート別心後遺症累積罹患率を急性期と後遺症期に分けて報告している[7]。免疫グロブリンが川崎病の治療薬として健康保険適用になったのが1990年であり，出生年コホート

別にみると，1990年生まれ以降は80%以上の患児に使用されており，それを境に心障害後遺症期累積罹患率は徐々に低下していると報告した。

今回は，出生年コホート別の川崎病心後遺症と心後遺症の種類別病変について，累積罹患率を求め，経年的な変動の傾向を調査した。全国調査の質問事項がいろいろ変更になっているため，今回の調査では，第15回調査以降で3歳時の累積罹患率を求めた。

種類別病変の分析に関しては，急性期において，各コホートで心後遺症全体のほぼ8割を冠動脈の拡大病変が占めており，拡大病変と瘤病変を合計すると88.8～94%と約9割になっていた。後遺症期になると，心障害後遺症期累積罹患率に対する比は，拡大病変が6割で，瘤病変が約3割と，瘤の占める割合が増えていることがわかった。さらに経年的な傾向をみると，拡大と瘤病変は相反する増減の変動をしていた。しかし，拡大と瘤の合計をとり，比較してみると，各コホートとも，全体の心後遺症累積罹患率に対する比は，後遺症期は87.3～92.7%であり，急性期も後遺症期もほぼ同じような約9割の率であった。このことは，川崎病が全身の血管炎を惹起する疾患であり，血管の狭窄傾向より膨張傾向が強い病変が主として惹起されることを再認識させられる結果となった。

心後遺症全体の変動については，心障害急性期累積罹患率は1998～2002年コホートまで低下傾向であったが，2003，2004年コホートで上昇し，心障害後遺症期累積罹患率も2000年まで低下傾向であったものが，2000～2002年と横ばいとなり，2003年から徐々に上昇傾向にあることに注目しなければならない。この全体の心後遺症罹患率の変動の主体を成すものは拡大病変と瘤病変であり，2003，2004年コホートに関して，拡大病変の増加が心障害急性期累積罹患率を押し上げていた。

一方，急性期から後遺症期への遺残率の比較では，拡大病変が　22.8～28.8%であるのに対して，瘤の遺残率は58.1～74.2%ぐらいと高く，差がみられた。また，それぞれの種類別病変の累積罹患率を川崎病全体の累積罹患率で除した発生率は，急性期の拡大病変が1997年コホートの15%から2004年の9.8%に減少し，瘤病変は2.9%から1.5%へと，それぞれ低下していた。心障害後遺症の発生率に関しては，治療法のガイドライン作成など全国的に画一化され[8]，2003年には免疫グロブリンの超大量静注療法（2 g／Kg）の健康保険適用があって[9]，下がってきているようであるが，川崎病自体の罹患者の増加が急であるためか[10～12]，出生年別の累積罹患率としては，2003，2004年と若干上昇してきているのではないかと考えられる。

巨大瘤の累積罹患率は急性期と後遺症期でほぼ同じであった。急性期の巨大瘤を示したものはほぼ後遺症期にも残存する可能性が高いと思われる。また，経年的にみると，低下傾向であったものが，2003，2004年コホートで上昇しており，冠動脈膨張傾向である急性期の拡大病変累積罹患率と同じ変動であった。

弁膜病変が近年，少しずつ累積罹患率が上昇してきているのには要注意である。特に，2003，2004年コホートにおいて増加しているのは，拡大病変や，瘤，巨大瘤の増加の時期と一致していた。

狭窄病変と心筋梗塞は率が低くて，分析が困難であるが，後遺症期の方が急性期より率が高いのが特徴のようである。血管腔の縮小性の変化は急性期より時間が経った後に現れやすいのであろうか。

これらの心障害の具体的病変の記載は，択一選択ではなく，重複の報告もある。しかし，1997年コホートでみると，重複例の割合は急性期で4.5%，後遺症期では7.0%であり，少数であった。

今回は10歳までの累積の50%と考えられた3歳時までの累積の比較で分析するしかなかったが，2004年コホートで出生数10万人あたり川崎病罹患者が524.4（約190人に1人）で，心障害後遺症期の残存者が20.9（約4,800人に1人），拡大病変残存者が13.9（約7,200人に1人），瘤病変残存者が4.5（約22,200人に1人）と判明した。

経年的には，川崎病累積罹患率が毎年上昇しているが，心後遺症の発生率は低下している。しかし，川崎病累積罹患率の上昇に引きずられて，心後遺症の累積罹患率は2003年以降，再び

上昇傾向を示しているようであった。具体的病変では，拡大や瘤病変が主体であることに変化はなかった。

これからも全国調査を継続して，5歳時や10歳時までの累積ができたコホートを増やすと，より正確な川崎病による心後遺症残存者の割合というものが判明すると思われる。さらなる川崎病全国調査の継続が必要である。

この論文の要旨は平成21年10月17日に第28回全国川崎病研究会にて，5歳時の累積データをもとに発表した。

文　献

1) 鮎沢　衛．診断の手引き：改訂5版．五十嵐隆，石井正浩．川崎病のすべて．東京：中山書店，2009：54-59.
2) 柳川　洋．過去16回の川崎病全国調査の概要．柳川　洋，中村好一，屋代真弓，他編．川崎病の疫学—30年間の総括—．東京：診断と治療社，2002：68-78.
3) 川崎病研究グループ．第19回川崎病全国調査成績．小児科診療　2008：71：165-176.
4) 屋代真弓．患者ファイルの種類と内容．柳川　洋，中村好一，他編．川崎病の疫学—30年間の総括—．東京：診断と治療社，2002：22-28.
5) 中村好一，川崎病疫学調査における個人情報保護に関する考察．柳川　洋，中村好一，他編．川崎病の疫学—30年間の総括—．東京：診断と治療社，2002：137-138.
6) 河合邦夫，屋代真弓，中村好一，他．出生年コホート別にみた川崎病累積罹患率，小児科診療　2008：71：151-155.
7) 河合邦夫，屋代真弓，中村好一，他．川崎病の出生年コホート別心後遺症累積罹患率，日本小児科学会雑誌　2009：113：1212-1218.
8) 2001～2002年度合同研究班．川崎病心臓血管後遺症の診断と治療に関するガイドライン．Circulation Journal　2003：67：1111-1173.
9) 牟田広実．疫学調査からみた急性期免疫グロブリン治療．五十嵐隆，石井正浩，他編．川崎病のすべて．東京：中山書店，2009：88-89.
10) 屋代真弓，中村好一，柳川　洋．川崎病疫学像の最近の推移1989～2004，日本小児科学会雑誌　2007：111：740-745.
11) Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan：results from the nationwide survey in 2005-2006. Journal of Epidemiology 2008；18 (4)：167-172.
12) Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan：results from the nationwide survey in 2007-2008. Journal of Epidemiology 2010；(in press).

〔Summary〕

Kawasaki disease (KD) is an acute type of systemic vasculitis associated with coronary artery involvement in infant.

The annual incidence of KD have been reported in KD nationwide surveys. However, for general physicians who are engaged in cardiac examinations at school, it is more important to know about the percentage of students and children who suffered from the cardiac sequelae of KD within a single school grade. Therefore, KD patients with cardiac sequelae (i.e. coronary giant aneurysm, aneurysmal changes, dilataion ,stenosis, myocadial infarction, cardiac valvular lesion.) were classified by their birth years ,and the cumulative number of patients (at the ages of 3 years) was expressed as the number per 100,000 individuals born each year.

In the 2004 cohort at 3 years of age, the number of the cumulative incidence rate of KD was 524 per 100,000 births, and it was on the increase year by year. Because of the rise in the cumulative incidence rate of KD, the cumulative incidence rate of acute stage cardiac sequelae, that of late stage cardiac sequelae, and that of coronary dilatative lesions in 2003, 2004 cohort turned to an upward trend from a tendency to decrease

〔Key words〕

kawasaki disease, birth-year cohort, cardiac sequelae, the cumulative incidence of acute stage cardiac sequelae, the cumulative incidence of late stage cardiac sequelae

Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008)

– Digest Version –

JCS Joint Working Group

Chair:
- Shunichi Ogawa, Department of Pediatrics, Nippon Medical School

Members:
- Teiji Akagi, Cardiac Intensive Care Unit, Okayama University Hospital
- Kiyoshi Baba, Department of Pediatrics, Osaka Developmental Rehabilitation Center
- Hisayoshi Fujiwara, Hyogo Prefectural Amagasaki Hospital
- Kenji Hamaoka, Department of Pediatric Cardiology and Nephrology, Kyoto Prefectural University of Medicine Graduate School of Medical Science
- Masahiro Ishii, Department of Pediatrics, Kitasato University
- Kensuke Karasawa, Department of Pediatrics, Nihon University School of Medicine
- Tsutomu Saji, First Department of Pediatrics, Toho University
- Tomoyoshi Sonobe, Department of Pediatrics, Japanese Red Cross Medical Center
- Atsuko Suzuki, Department of Pediatrics, Tokyo Teishin Hospital

Collaborators:
- Mamoru Ayusawa, Department of Pediatrics, Nihon University School of Medicine
- Ryuji Fukazawa, Department of Pediatrics, Nippon Medical School
- Kazuhiko Nishigaki, Second Department of Internal Medicine, Gifu University
- Hirotaro Ogino, Department of Pediatrics, Kansai Medical University
- Tomoo Okada, Department of Pediatrics, Nihon University School of Medicine

Independent Assessment Committee:
- Shigeyuki Echigo, Echigo Clinic
- Makoto Nakazawa, Pediatric and Lifelong Congenital Cardiology Institute, Southern Tohoku General Hospital
- Masami Ochi, Division of Cardiovascular Surgery, Nippon Medical School
- Tetsu Yamaguchi, Toranomon Hospital

(The affiliations of the members are as of March 2010)

Circulation Journal

Vol. 74 No. 9 September 2010

(Pages 1989–2020)

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008)

– Digest Version –

JCS Joint Working Group

Table of Contents

(*Circ J* 2010; **74:** 1989–2020)

Released online August 18, 2010

Mailing address: Scientific Committee of the Japanese Circulation Society, 8th Floor CUBE OIKE Bldg., 599 Bano-cho, Karasuma Aneyakoji, Nakagyo-ku, Kyoto 604-8172, Japan. E-mail: meeting@j-circ.or.jp

This English language document is a revised digest version of Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease reported at the Japanese Circulation Society Joint Working Groups performed in 2007. (website http://www.j-circ.or.jp/guideline/pdf/JCS2008_ogawasy_d.pdf)

Joint Working Groups: The Japanese Circulation Society, The Japanese Association for Thoracic Surgery, The Japan Pediatric Society, The Japanese Society of Pediatric Cardiology and Cardiac Surgery, The Japanese College of Cardiology

ISSN-1346-9843 doi:10.1253/circj.CJ-10-74-0903

Introduction of the Revised Guidelines

More than forty years have passed since 1967, when the first case series of Kawasaki disease was reported.[1] Currently, more than half of the patients diagnosed with Kawasaki disease are 16 years of age or older. In Japan, Kawasaki disease is now managed not only by pediatricians but also by internists. As this timeline suggests, it is expected that more than half of the patients with cardiovascular sequelae of Kawasaki disease have reached adulthood. However, since Kawasaki disease develops most frequently by around 1 year of age, many internists are still not familiar with it (**Table 1**). The main cardiovascular disease caused by Kawasaki disease is vasculitis, and in this respect patients with this disease differ significantly from other adult patients with arteriosclerosis and/or hypertension. Since the number of adult patients with a history of Kawasaki disease will increase over time, pediatric cardiologists need to accurately provide their findings on Kawasaki disease to cardiovascular internists. Reliable means are needed to ensure appropriate diagnosis, treatment, and determination of the prognosis of patients with cardiovascular sequelae in Kawasaki disease. We hope the present guidelines will help healthcare professionals diagnose and treat their patients with Kawasaki disease.

No major additions or corrections of the revised guidelines presented here have been made. The present guidelines basically follow the previous version of the guidelines. However, since the number of adult patients with coronary artery lesions and a history of Kawasaki disease is growing increasingly larger over time, in the present guidelines additional descriptions are included of the risk of development of arteriosclerosis, mechanism of development of arteriosclerosis, and prevention and treatment of arteriosclerosis in patients with a history of Kawasaki disease, particularly those with coronary artery lesions. The recent advancement of diagnostic imaging techniques has been impressive, and there are many techniques useful in the diagnosis and treatment of coronary artery lesions due to Kawasaki disease. The present

Table 1. Diagnostic Guidelines of Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome)

This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. Principal symptoms

1. Fever persisting 5 days or more (inclusive of those cases in whom the fever has subsided before the 5th day in response to therapy)
2. Bilateral conjunctival congestion
3. Changes of lips and oral cavity: Redding of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
4. Polymorphous exanthema
5. Changes of peripheral extremities:
   (Acute phase): Redding of palms and soles, Indurative edema
   (Convalescent phase): Membranous desquamation from fingertips
6. Acute nonpurulent cervical lymphadenopathy

At least five items of 1 to 6 should be satisfied for diagnosis of Kawasaki disease.
However, patients with four items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm or dilatation is recognized by two-dimensional (2D) echocardiography or coronary angiography.

B. Other significant symptoms of findings

The following symptoms and findings should be considered in the clinical evaluation of suspected patients.

1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage QRS complexes, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly), 2D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (axillary, etc.), angina pectoris or myocardial infarction
2. Gastrointestinal (GI) tract: Diarrhea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
3. Blood: Leukocytosis with shift to the left, thrombocytosis, increased erythrocyte sedimentation rate (ESR), positive C-reactive protein (CRP), hypoalbuminemia, increased α2-globulin, slight decrease in erythrocyte and hemoglobin levels
4. Urine: Proteinuria, increase of leukocytes in urine sediment
5. Skin: Redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the finger nails
6. Respiratory: Cough, rhinorrhea, abnormal shadow on chest X-ray
7. Joint: Pain, swelling
8. Neurological: Cerebrospinal fluid (CSF) pleocytosis, convulsion, unconsciousness, facial palsy, paralysis of the extremities

Remarks

1. For item 5 under principal symptoms, the convalescent phase is considered important.
2. Nonpurulent cervical lymphadenopathy is less frequently encountered (approximately 65%) than other principal symptoms during the acute phase.
3. Male: Female ratio: 1.3 to 1.5:1, patients under 5 years of age: 80 to 85%, fatality rate: 0.1%
4. Recurrence rate: 2 to 3%, proportion of siblings cases: 1 to 2%
5. Approximately 10% of the total cases do not fulfill five of the six principal symptoms, in which other diseases can be excluded and Kawasaki disease is suspected. In some of these patients coronary aneurysms (including so-called coronary artery ectasia) have been confirmed.

Prepared by the Kawasaki Disease Research Group of the Ministry of Health, Labor, and Welfare, 5th revised edition.

Table 2. Classification of Severity of Cardiovascular Lesions in Kawasaki Disease

(a) Classification of coronary aneurysms during the acute phase

Small aneurysms (ANs) or dilatation (Dil): localized dilatation with ≤4 mm internal diameter

In children ≥5 years of age, the internal diameter of a segment measures <1.5 times that of an adjacent segment

Medium aneurysms (ANm): aneurysms with an internal diameter from >4 mm to ≤8 mm

In children ≥5 years of age, the internal diameter of a segment measures 1.5 to 4 times that of an adjacent segment

Giant aneurysms (ANl): aneurysms with an internal diameter of >8 mm

In children ≥5 years of age, the internal diameter of a segment measures >4 times that of an adjacent segment

(b) Severity classification

The severity of Kawasaki disease is classified into the following 5 grades on the basis of findings of echocardiography and selective coronary angiography or other methods:

I. No coronary dilatation: patients with no coronary dilatation including those in the acute phase

II. Transient coronary dilatation during the acute phase: patients with slight and transient coronary dilatation which typically subsides within 30 days after onset

III. Regression: patients who still exhibit coronary aneurysms meeting the criteria for dilatation or more severe change on day 30 after onset, despite complete disappearance of changes in the bilateral coronary artery systems during the first year after onset, and who do not meet the criteria for Group V

IV. Remaining coronary aneurysm: patients in whom unilateral or bilateral coronary aneurysms are detected by coronary angiography in the second year or later and who do not meet the criteria for Group V

V. Coronary stenotic lesions: patients with coronary stenotic lesions detected by coronary angiography

(a) Patients without ischemic findings: patients without ischemic signs/symptoms detectable by laboratory tests or other examinations

(b) Patients with ischemic findings: patients with ischemic signs/symptoms detectable by laboratory tests or other examinations

Other clinical symptoms of findings: When patients have moderate or severe valvular disease, heart failure, severe arrhythmia, or other cardiac disease, such conditions should be described in addition to the severity of Kawasaki disease.

guidelines thus describe in detail current knowledge on diagnostic imaging techniques used to evaluate coronary artery lesions. We also discuss the genetic background of Kawasaki disease, although findings regarding this still limited.

We previously discussed the classification of coronary artery lesions during the acute phase of Kawasaki disease. Although the criteria for small aneurysms and giant aneurysms were slightly questioned, we decided that no modifications of the criteria needed to be made, based on the opinions of members and collaborators such as that no new evidence have been provided on this matter, and that the classification may not be revised in the present guidelines because it will not affect the contents of the present guidelines for the diagnosis and treatment of cardiovascular sequelae in Kawasaki disease. We used the conventional classification to prepare the present guidelines (**Table 2**).

Although the present guidelines are based in principle on available evidence, the diagnosis and treatment of sequelae in Kawasaki disease are often based on case reports. Emphasis was therefore placed on case reports in the present guidelines as well. **Table 3** lists the criteria for levels of recommendations on the procedure and treatment of cardiovascular sequelae in Kawasaki disease.

Table 3. Levels of Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of a procedure or treatment.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and may in some cases be harmful.

I Current Epidemiology of Kawasaki Disease, and Advancement in and Topics Related to Acute Phase Treatment

1. Current Epidemiology of Kawasaki Disease

According to the 19th national survey on Kawasaki disease (2005 to 2006),[2] the number of patients diagnosed was 10,041 in 2005 and 10,434 in 2006, yielding a total of 20,475 patients. The mean prevalence during the 2-year survey period was 184.6 patients/100,000 children 0 to 4 years of age (male 209.3, female 158.6). The total number of patients with Kawasaki disease including those patients reported in the 19th national survey is 225,682 (male 130,827, female 94,855) as of December 31, 2006. About 90,000 patients were ≥20 years of age as of January 2006.[3]

2. Mortality and Prognosis of Patients With Kawasaki Disease

The mortality of patients with Kawasaki disease has gradually decreased, from 0.13% in 1989 to 0.01% in the latest survey.

In a cohort study of 6,576 patients followed for about 20

years,[4] the standardized mortality ratio (SMR) was 1.14 overall and 0.71 in patients after the acute phase. The mortality rate in male patients with cardiac sequelae in Kawasaki disease was 2.55, and significantly higher than the overall rate.

3. Advancement in Intravenous Immunoglobulin (IVIG) Therapy

During the acute phase, about 86% of patients received IVIG therapy in the 19th national survey.[2] Among patients undergoing initial IVIG therapy, 16.2% received an additional IVIG therapy after the initial therapy, and 4.5% of patients received steroids (including patients receiving additional IVIG therapy and those receiving a combination of IVIG and steroids). Pulse steroid therapy was performed in 3.0% of patients and non-pulse steroid therapy in 2.5% (including patients undergoing both pulse therapy and non-pulse therapy).

4. Changes Over Time in the Incidence of Coronary Artery Lesion

The prevalence of coronary artery lesion during the acute phase has decreased over time: 18.1% in 1997 to 2000 (coronary dilatation 14.7%, aneurysm 2.9%, giant aneurysm 0.50%), 14.8% in 2001 to 2004 (coronary dilatation 11.6%, aneurysm 1.9%, giant aneurysm 0.36%),[5] and 11.9% in the 19th survey (coronary dilatation 10.1%, aneurysm 1.5%, giant aneurysm 0.35%).[2]

The prevalence of coronary artery lesion observed as sequelae in Kawasaki disease has also decreased, from 6.2% in 1997 to 2000 (coronary dilatation 3.9%, aneurysm 1.9%, giant aneurysm 0.46%), to 4.5% in 2001 to 2004 (coronary dilatation 2.8%, aneurysm 1.3%, giant aneurysm 0.33%), and 3.7% in the 19th survey (coronary dilatation 2.3%, aneurysm 1.0%, giant aneurysm 0.35%). The improvement of clinical results may be explained by the increase in frequency of use of single-dose treatment with immunogloblin 2 g/kg from 8% to 68%.

5. Advancement in Treatment for Patients Not Responding to IVIG Therapy

It is important to treat patients not responding to initial IVIG therapy, who account for about 15% of children with Kawasaki disease, and additional treatments with IVIG, steroid, ulinastatin, and plasmapheresis has been performed for them. Although immunosuppressive agents, such as cyclosporine and infliximab are also used currently, the efficacy and safety of these drugs in the treatment of Kawasaki disease have yet to be established.

6. Problems With Incomplete (Atypical) Kawasaki Disease

The incidence of coronary artery lesions in patients exhibiting 4 principal symptoms of Kawasaki disease is slightly higher than that in patients with 5 to 6 principal symptoms.[6] Presentation of a small number of principal symptoms does not necessarily indicate mild disease. Patients with at least 4 principal symptoms require treatment identical to that for patients with complete (typical) Kawasaki disease, and patients with ≤3 principal symptoms should be treated similarly to those with complete Kawasaki disease.

II Pathology, Pathophysiology, and Natural History of Cardiac Sequelae in Kawasaki Disease

1. Coronary Artery Lesions

The incidence of coronary aneurysm as a sequelae of Kawasaki disease was 16.7% in 1983, when aspirin was the main component of acute phase treatment, but decreased to 3.8% in 2007 as the use of high-dose gamma globulin therapy increased.[2] The mortality rate of children with Kawasaki disease was above 1% by 1974, but decreased to around 0.1% in 1990s and is currently 0.01%.[2]

1 Development of Coronary Aneurysms

Coronary artery lesions are observed during the initial acute phase of Kawasaki disease by echocardiography in all patients as increased echo intensity of the coronary artery wall an average of 5.4 days after onset.[7] Coronary dilatation subsides during the initial acute phase, ie, within 30 days after onset, and is referred to as transient coronary dilatation,[7] while coronary aneurysms persisting during the convalescence phase or later are considered sequelae of Kawasaki disease. The incidences of coronary sequelae have decreased to 10.09%, 1.49%, and 0.35% in the case of coronary dilatation, aneurysms, and giant aneurysms, respectively.[2] It is important to examine for persistent aneurysms using echocardiography during the early stage and about 30 days after the onset of Kawasaki disease.

2 Prognosis (Table 2 and Table 4)

(1) Reduction and Regression of Aneurysms

Coronary aneurysms remaining ≥30 days after the onset of Kawasaki disease typically decrease in size during the convalescence phase or later. "Regression" of coronary aneurysms, ie, disappearance of abnormal findings on coronary angiography (CAG), often occurs within 1 to 2 years after onset and typically occurs in the case of small or medium aneurysms.[8] This regression has been reported to occur in 32[9] to 50%[10] of patients. It has been reported that patients may develop stenosis of vessels[11] that have exhibited regression, decrease in coronary diastolic function,[12] abnormal vascular endothelial function, and substantial intimal hyperplasia,[12–14] which have been suggested to lead to juvenile arteriosclerosis. Patients should thus be followed up even after regression of coronary aneurysms.[15]

(2) Occlusion of Aneurysms

Medium and giant aneurysms are often associated with thrombotic occlusion in the relatively early stage of Kawasaki

Table 4. Classification of Coronary Artery Lesions by Angiographic Findings

- Dilatation lesions: DL (ANl, ANm, ANs, or Dil, as defined in echocardiography-based classification [**Table 2**])
- Stenotic lesions: SL
- Occlusion: OC, 100% SL
- Segmental stenosis: SS [recanalized vessel] (See **Figure 1**)
  - A. Braid-like lesion: multiple regions of neovascularizations within the thrombotic occlusion
  - B. Bridging lesion: development of nutrient arteries distal to an occluded aneurysm
  - C. Pericoronary artery communication: anterograde blood flow with a communication of two points in one coronary artery via an existing vessel
- Local stenosis: LS

Subcommittee on Standardization of Coronary Artery Lesions due to Kawasaki Disease, "the Kawasaki Disease Research Group", Ministry of Health and Welfare, 1983.

disease. While coronary occlusions are associated with myocardial infarction and sudden death, approximately two-thirds patients with them are asymptomatic.[16] It is typical of Kawasaki disease that coronary occlusion is followed by the development of recanalized vessels and collateral flows which significantly improve findings of myocardial ischemia.[17] However, patients may often suffer symptoms of myocardial ischemia during adolescence, and may require bypass surgery or develop heart failure and arrhythmias.

(3) Recanalization (Segmental Stenosis)

Neovascularization considered to represent recanalization after occlusion is referred to as segmental stenosis. Segmental stenosis is observed in 15% of patients with coronary artery lesions due to Kawasaki disease, and occurs in the right coronary artery in 90% of such patients[16]; occlusion and recanalization in the right coronary artery are considered more common. Angiographic findings of segmental stenosis are classified into three types according to their pathophysiology, time of onset, and prognosis[17] (**Figure 1**).

(4) Localized Stenosis

During the period up to 10 to 21 years after onset, localized stenoses of ≥75% vessel diameter develop in 4.7 to 12% of patients with coronary artery lesions, and often occur in the proximal segment or the main trunk of the left anterior descending artery.[18] Although progression to stenosis is more common in the case of giant aneurysms, it has been suggested that even small aneurysms with a diameter of 5 to 6 mm on angiography may progress to stenosis during long-term follow-up.[9] Evaluation with intravascular ultrasound (IVUS) has revealed intimal hyperplasia in aneurysms with an internal diameter of >4 mm, which may progress to stenosis.[19]

(5) Coronary Arteries Without Aneurysm Formation

Slight or moderate intimal hyperplasia in coronary arteries without aneurysm formation has been reported in patients with Kawasaki disease,[12,14] and whether a history of Kawasaki disease is a risk factor for development of atherosclerotic lesions has been discussed.

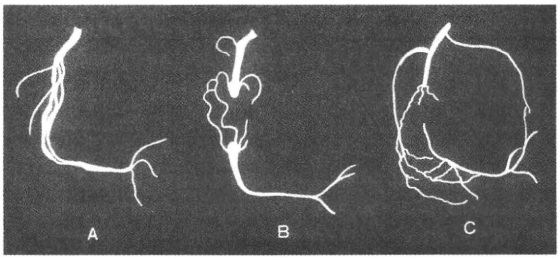

Figure 1. Subtypes of segmental stenosis.

Table 5. Characteristics of Myocarditis During the Acute Phase of Kawasaki Disease

Myocarditis during the acute phase of Kawasaki disease

- is often transient
- is often associated with a slight decrease in left ventricular ejection fraction
- is often associated with transient pericardial effusion
- is associated with transient abnormalities of all valves, among which slight mitral insufficiency and aortic insufficiency may persist
- is rarely associated with severe myocarditis.

2. Myocardial Injury

Myocardial injury is classified mainly into two types: inflammatory myocardial injury associated with myocarditis or valvulitis during the acute phase, and ischemic myocardial injury secondary to coronary aneurysms or microcirculation disorder due to coronary arteritis.

1 Inflammatory Lesions

Interstitial myocarditis and pericarditis are major inflammatory heart diseases associated with Kawasaki disease. The presence of myocarditis during the acute phase has been detected with gallium (Ga)-67 myocardial scintigraphy.[20] Cell infiltration mainly by monocytes is a main pathological finding, while degeneration and necrosis of myocytes are rare. **Table 5** lists the characteristics of myocarditis in Kawasaki disease.

2 Ischemic Lesions

Acute myocardial infarction (AMI) due to stenotic lesions adjacent to coronary aneurysms caused by severe coronary arteritis tends to develop during the second week after onset or later. Progression of coronary aneurysms to stenotic lesions is more prevalent in aneurysms with an internal diameter of ≥6 mm, and is especially prevalent in giant aneurysms with a diameter of ≥8 mm. Chronic myocardial infarction is observed more often after the first 7 weeks of disease, following the acute phase.

3 Lesions in the Conducting System

During the acute phase, inflammation of the conducting system is observed, and transient atrioventricular block, premature ventricular contraction, supraventricular tachycardia, or ventricular tachycardia may develop as clinical manifestations of injury to the conducting system.

3. Valvular Disease

Slight and transient mitral, tricuspid, or pulmonary valve insufficiency is often observed by Doppler echocardiography during the acute phase of Kawasaki disease, and aortic valve insufficiency is also observed in rare cases.[21] In addition to regurgitation due to myocarditis and valvulitis during the acute phase, regurgitation may also develop during the remote phase due to thickness or deformation of valves with fibrosis after valvulitis, or to papillary muscle dysfunction caused by ischemia[22–24] (**Figure 2**). The incidence of valvular disease is reported to be 1.88% during the acute phase and 0.41% or later.[2]

4. Arteriosclerosis (Especially Progression to Atherosclerosis)

The progression of vessel disorders due to Kawasaki disease, and especially that of coronary artery lesions to sclerotic lesions, has been described in detail.[14,25–29] Recent clinical studies have revealed that abnormal diastolic function of peripheral vessels and changes in endothelial cell biomarkers of vascular endothelial dysfunction are present during the remote phase regardless of the presence or absence of coronary artery lesions.[30–32] However, there is no clinical evidence clearly indicating whether the incidence of atherosclerosis, a finding of lifestyle-related diseases commonly observed in adults, is higher in individuals with a history of Kawasaki disease. Long-term, large-scale, continuous clinical studies will be needed to answer this question.

Careful and detailed investigations of the development and progression of arteriosclerotic lesions after Kawasaki disease are needed to clarify the mechanisms underlying them and determine how to prevent the development/progression of such lesions, in ensuring appropriate long-term management of patients.

5. Non-Coronary Vessel Disorders

Aneurysms of the axillary arteries, femoral arteries, iliac arteries, renal arteries, abdominal aorta, and internal mammary arteries have been observed in rare cases (0.6[33] to 2%[34]), and all patients with peripheral aneurysms in these arteries have large coronary aneurysms. Cases of necrotic lesions of the fingers, cerebral infarction due to cerebrovascular disorders, renovascular hypertension, shock due to rupture of femoral arteries, replacement of large abdominal aneurysms with vascular prostheses, and coating of aneurysms have been reported in patients with a history of Kawasaki disease. Although in many cases aneurysms in the axillary arteries and other vessels regress within 1 to 2 years, a case of abrupt occlusion after 35 years has been reported.[35] Patients with aneurysms of the peripheral arteries should thus be followed for a long period of time.

6. Summary of Pathology, Pathophysiology, and Natural History of Cardiac Sequelae

1 Coronary Artery Lesions

Although significant infiltration of inflammatory cells in the coronary arteries during the acute phase of Kawasaki disease regresses over time, a large number of inflammatory cells may remain in the intima, and endarteritis may persist for a long period of time even after remission of clinical symptoms.[36,37] During the remote phase, vascular smooth muscle cells continue to multiply actively at the inlet and outlet of the aneurysm,[29] and concentric intimal hyperplasia may induce stenosis or occlusion. When an aneurysm becomes clogged by a clot, a new artery with multiple lumens is often formed through the clot. The prognosis in such cases of myocardial ischemia is thus often fair.[17] However, such spontaneous recanalization develops only when sudden death or severe myocardial infarction does not occur at the time of occlusion. Patients with medium or giant aneurysms and those with progressive localized stenosis are continuously at risk of sudden death and/or myocardial infarction. It is therefore believed

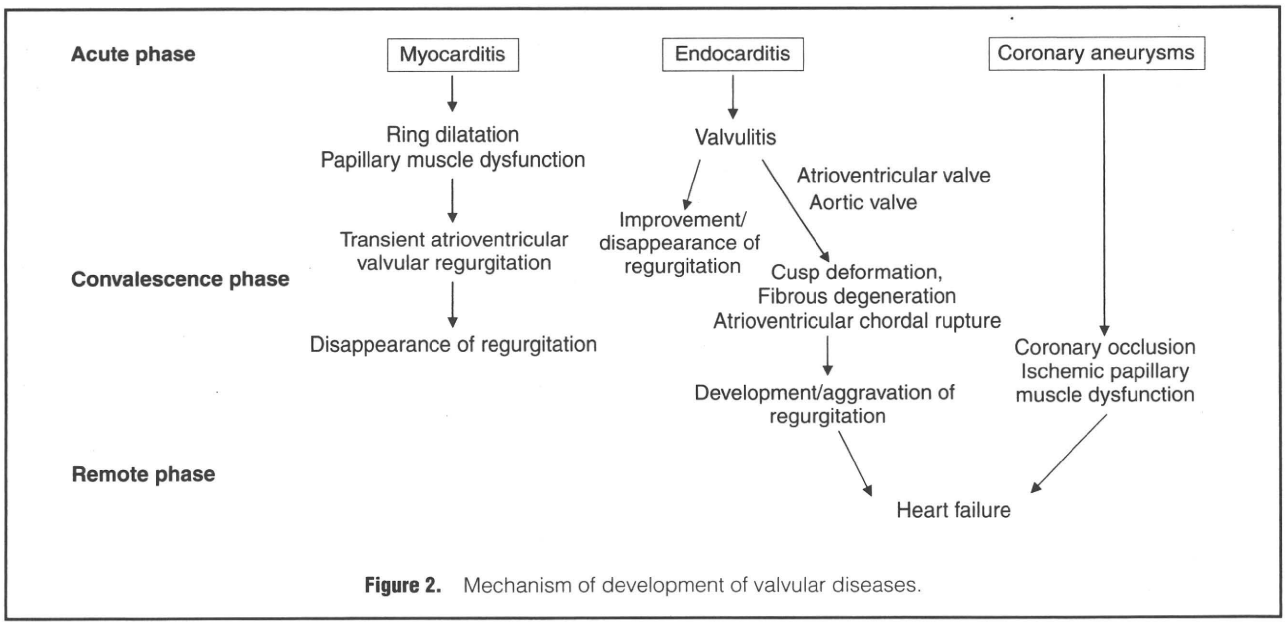

Figure 2. Mechanism of development of valvular diseases.

that such patients be followed for life with frequent selective CAG, magnetic resonance imaging (MRI),[36] and/or multi-row detector computed tomography (MDCT)[38] to monitor changes in the morphology of coronary arteries.

2 Myocarditis, Endocarditis, Valvulitis, and Pericarditis

These inflammatory cardiac diseases, which are often asymptomatic, are quite prevalent during the acute phase.[39] They are often mild in severity throughout the course of disease, though heart failure, cardiac tamponade, and death due to arrhythmia induced by inflammation of atrioventricular and/or

Table 6. Major Reports of Studies of Gene Polymorphism Associated With Kawasaki Disease

Analysis	SNP	No. of patients	Ethnic group	Results	Reported by
*Susceptibility to KD		78 KD sibling pairs	Japanese	Linkage analysis of siblings of KD patients. High linkage disequilibrium was noted in 12q24, 4q35, 5q34, 6q27, 7q15, 8q24, 18q23, 19q13, Xp22, and Xq27.	Onouchi Y, et al[41]
*Susceptibility to KD Risk for CAL	*ITPKC*	78 KD sibling pairs Case control study in 276 KD patients and 282 controls	Japanese Americans	Linkage analysis of siblings of KD patients. 1,222 SNPs in 19q13.2-13.3 with linkage disequilibrium 3SNPs, from which ITPKC was selected. ITPKC plays a role in the negative control of IL-2 expression. Expression of ITPKC was low in C allele, and expression of IL-2 was increased. In Japanese participants, the incidence of coronary artery disorder was 2.05-fold higher with the C allele.	Onouchi Y, et al[42]
Susceptibility to KD	*CD40L*	427 KD patients 476 controls	Japanese	CD40L gene was screened to detect 22 SNP. IVS4+121 A>G in intron 4. G allele was high in KD.	Onouchi Y, et al[43]
Susceptibility to KD	*CCR3-CCR2-CCR5 cluster*	170 KD patients 300 controls	German Caucasians	Two haplotypes of the CCR3-CCR2-CCR5 gene cluster appear to be at risk for KD, and one to be a protective haplotype.	Breunis WB, et al[44]
Susceptibility to KD	*CCR5 CCL3L1*	160 KD families	Americans	An inverse relationship between the worldwide distribution of CCR5 Δ32 allele and the incidence of KD was observed. HHG*2, the CCR5 Δ32-containing haplotype of CCR5, was associated with decreased susceptibility to KD. Analysis of CCR5 ligands and CCL3L1 gene dose stratum revealed that Individuals who possessed both HHG*2 and 2 copies of CCL3L1 had a nearly 80% lower risk of developing KD.	Burns JC, et al[45]
Susceptibility to KD	*VEGF*	170 KD patients 300 controls	German Caucasians	The VEGF haplotype CGCC (-259A/C, Ex1+405G/C, Ex1-73C/T, 236bp3'STP CC) was correlated with susceptibility to KD.	Breunis WB, et al[46]
Susceptibility to KD	*IL-4*	220 KD families (trio)	Americans Canadians	TD analysis was performed for 98 SNPs of 58 genes in a cohort of 209 KD families (trio). PON1, GPRK2L, IL-4, TGF-beta, and GC were screened. Only IL-4 was significant in another cohort. Haplotype analysis of genes near IL-4 did not reveal any correlations stronger than for IL-4. No correlation with CAL was noted. The C allele of the IL-4 C-589G was correlated with susceptibility to KD.	Burns JC, et al[47]
Risk for CAL	*TIMP-2*	208 KD patients 184 controls	Japanese	Expression of TIMP-2 in PBMCs was high in the CAL group. Analysis of 5 SNP in the 5' flanking region revealed significantly higher expressions of -806T>C, -417G>C, -177C>G in the CAL group for both genotype and allele type. In the CCCAT haplotype, a significant decrease in expression of TIMP-2 was confirmed. CCCAT haplotype was significantly lower in the CAL group.	Furuno K, et al[48]
Risk for CAL	*ACE*	246 KD patients 147 controls	Japanese	The presence of the ACE I/D D allele and AT1R 1166A/C C allele increased the incidence of coronary stenosis 2.71-fold.	Fukazawa R, et al[49]
Disease severity	*MCP-1, CCR2*	184 KD patients	Japanese	The G/G allele of the MCP-1-2518C/G was associated with long duration of fever, and tended to be intractable to immunoglobulin therapy.	Fukazawa R, et al[50]

*Comprehensive gene expression analysis.
KD, Kawasaki disease; CAL, coronary artery lesion; SNP, single nucleotide polymorphism; ITPKC, inositol 1,4,5-triphosphate 3-kinase C; CD40L, cluster differentiation 40 ligand; CCR, chemokine CC motif receptor; CCL, chemokine CC motif ligand; VEGF, vascular endothelial growth factor; IL, interleukin; TIMP-2, tissue inhibitor of metalloproteinase-2; ACE, angiotensin converting enzyme; MCP-1, monocyte chemoattractant protein-1; PON1, paraoxonase; TGF, transforming growth factor; PBMCs, peripheral blood mononuclear cells.

sinoatrial conducting system may occur in rare cases.

3 Ischemic Myocardial Injury

Although ischemic heart disease is the major cause of death of patients with Kawasaki disease, many such deaths occur suddenly, and the number of patients exhibiting histopathological findings of AMI at autopsy is thus small.[39] However, lesions of chronic myocardial infarction are often observed at autopsy in patients[16] who did not experience cardiac episodes or exhibit findings of ischemia.[39,40]

7. Genetic Background

Although Kawasaki disease is not a genetic disease, the possibility of a genetic predisposition toward it has been suggested by the findings that (1) the incidence of Kawasaki disease in Japan is 10 to 20-fold that in Western countries,[51] (2) the incidence of Kawasaki disease among siblings of patients is about 10-fold that in the general population,[52] and (3) the incidence in offspring of parents with a history of Kawasaki disease is about twice that in the general population.[53]

There have been reports suggesting that genetic polymorphisms are associated with "susceptibility to Kawasaki disease", "risk for abnormal changes in the coronary arteries", and "severity of disease and responses to immunoglobulin therapy". **Table 6** lists case-control studies conducted after comprehensive analysis of genes associated with Kawasaki disease, and case-control studies on previously specified genes in at least 150 patients.

III Examinations

1. Blood Tests

1 Myocardial Infarction

Since no reference values for diagnosis have been established for blood biochemical markers of AMI in children, reference values in adult patients should be used instead.

Blood biochemical markers of injury to cardiomyocytes include creatine kinase (CK) located in the cytoplasmic soluble fraction, CK-myocardial band (MB), myoglobin, heart-type fatty acid-binding protein (H-FABP), myosin light chain (MLC) in myofibril, and troponin T and troponin I (TnT, TnI). It is important to use appropriate markers based on the duration of time after onset of myocardial infarction.

Myoglobin and H-FABP (with H-FABP ≥6.2 ng/mL classified as positive) are useful in the diagnosis of myocardial infarction immediately after onset,[54,55] while CK-MB and TnT (with TnT ≥0.10 ng/mL classified as positive) are useful for the diagnosis of myocardial infarction ≥6 hours after onset. The principal biochemical markers of myocardial infarction are CK-MB and TnT[54] (**Table 7**).

2 Arteriosclerosis

The criteria for diagnosis of metabolic syndrome, which include hyperlipidemia and insulin resistance, are important in the diagnosis of arteriosclerosis. In the diagnosis of hyperlipidemia, levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride (TG) are commonly used. Homocysteine level has attracted attention as an independent risk factor for arteriosclerosis. Since metabolic syndrome, for which visceral fat deposition is one of the principal criteria, may often lead to the development of type 2 diabetes and cardiovascular diseases in later life, it has been proposed that abdominal obesity and metabolic syndrome should be cared early in life.

Table 8 lists the criteria for diagnosis of metabolic syndrome in children in Japan, **Table 9** lists the reference values of serum lipid levels in children, and **Table 10** lists the reference values of markers of hyperlipidemia in adults with a history of Kawasaki disease.

2. Physiological Examinations (ECG)

1 ECG at Rest

During the acute phase of Kawasaki disease, the ECG reveals findings suggestive of myocardial injury and abnormal repolarization such as prolonged PR interval, deep Q waves, prolonged QT interval, low voltage, ST-T changes, and arrhythmias.[56,58]

When myocardial infarction occurs in patients who still have coronary artery lesions, especially giant coronary aneurysms, during the remote phase, ST-T changes and abnormal Q waves that are consistent with the lesion of infarction are observed.[59]

2 Holter ECG

Holter ECG recording is worthwhile in patients complaining of frequent chest pain, chest discomfort, and/or palpitations. Patients with stenosis or giant aneurysms should undergo Holter ECG recording at least once to determine whether ischemic findings are present or development of high-risk arrhythmias is possible.

3 Stress ECG

(1) Exercise ECG

a) Double or Triple Master's Two-Step Test

Although it has been reported that the Master's two-step test can be routinely performed from infancy, and may provide a load equivalent to that observed during treadmill testing in terms of oxygen consumption in preschool children 4 to 6 years of age,[60] exercise ECG cannot detect abnormal findings in patients without severe ischemia.

b) Treadmill Test and Ergometer Stress Test

Treadmill tests and ergometer stress tests can be administered to school-age or older children, though their sensitivity in detecting ischemic findings is less than that of myocardial scintigraphy. It has therefore been recommended that pharmacological stress be added to increase the rate of detection, or that signal-averaged ECG be used.

(2) Pharmacological Stress Tests and Body Surface Potential Mapping

It has been reported that dipyridamole[61] or dobutamine stress

Table 7. Blood Biochemical Markers of Acute Myocardial Infarction (AMI)

Marker	Strengths	Weaknesses	Clinical use
CK-MB	1) Rapid and accurate test 2) Reinfarction can be detected promptly	1) Low myocardial specificity (specificity for AMI is low in patients with musculoskeletal disorder) 2) Low detection rate within 6 hours after onset	CK-MB is one of the principle biochemical markers, and can be used as a standard test in almost all institutions
Myoglobin	1) Detectable 1 to 2 hours immediatery after onset 2) Highly sensitive 3) Reperfusion can be detected	1) Poor myocardial specificity 2) Since the level returns to normal in 1 to 2 days after onset, it cannot be detected in patients who present late after AMI	Due to poor myocardial specificity, AMI cannot be diagnosed with myoglobin alone
H-FABP	1) Detectable 1 to 2 hours immediatery after onset 2) Infarct size can be estimated 3) Reperfusion can be detected	Rapid test kits are available. It is highly sensitive during the early diagnosis, but its specificity is relatively low	Rapid test kits are available throughout Japan and useful in early diagnosis
TnT	1) Highly sensitive and highly specific 2) Diagnosis is possible 8 to 12 hours after onset 3) Diagnosis is possible when testing is performed in the first 2 weeks after onset 4) Prompt diagnosis is possible with rapid test kits 5) Reperfusion can be detected	1) Sensitivity is low within 6 hours after onset (Retest 8 to 12 hours after onset) 2) Sensitivity to late-onset small reinfarction is low	Rapid test kits are available throughout Japan, and TnT is a principle biochemical marker
MLC	1) Detectable 4 to 6 hours after onset 2) Diagnosis is possible when testing in the first 2 weeks after onset	1) Sensitivity is relatively low 2) MLC is excreted renally and may be abnormal in patients with renal failure	Rapid diagnostic tests are not available

CK-MB, creatine kinase-myocardial band; H-FABP, heart-type fatty acid-binding protein; TnT, troponin T, MLC; myosin light chain.

Table 8. Criteria for Diagnosis of Metabolic Syndrome in Japanese Children 6 to 15 Years of Age (Final Draft In 2006)

Children meeting (1) and at least 2 of items (2) to (4) should be diagnosed with metabolic syndrome.

(1) Abdominal girth	≥80 cm (note)
(2) Serum lipid	
Triglyceride	≥120 mg/dL
and/or	
HDL cholesterol	<40 mg/dL
(3) Blood pressure	
Systolic pressure	≥125 mmHg
and/or	
Diastolic pressure	≥70 mmHg
(4) Fasting blood glucose	≥100 mg/dL

Note: Children with an waist-to-height ratio of ≥0.5 fulfill item (1). In elementary school children (6 to 12 years of age), those with an abdominal girth of ≥75 cm should be considered to fulfill item (1).
HDL, high-density lipoprotein.

Table 9. Criteria for Diagnosis of Pediatric Hyperlipidemia (Serum Lipid levels in Fasting Blood)[56]

Total cholesterol (mg/dL)	
Normal	<190
Borderline	190 to 219
Abnormal	≥220
LDL cholesterol (mg/dL)	
Normal	<110
Borderline	110 to 139
Abnormal	≥140
HDL cholesterol (mg/dL)	
Cut-off value	40
Triglyceride (mg/dL)	
Cut-off value	140

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 10. Criteria for Management of Hyperlipidemia in Adult Japanese for the Prevention and Treatment of Coronary Artery Disease[57]

Hypercholesterolemia	
Total cholesterol	≥220 mg/dL
Hyper LDL cholesterolemia	
LDL cholesterol	≥140 mg/dL
Hypo HDL cholesterolemia	
HDL cholesterol	<40 mg/dL
Hypertriglyceridemia	
Triglyceride	≥150 mg/dL

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

tests[62,63] using body surface potential mapping are useful in patients with myocardial ischemia due to Kawasaki disease with or without significant stenosis, including infants in whom exercise stress testing is not feasible.

(3) Electrophysiological Tests

Studies of patients with a history of Kawasaki disease who underwent electrophysiological evaluation with intracardiac catheters have revealed that the prevalence of abnormal sinus or atrioventricular nodal function is significantly higher in patients with than in those without cardiac sequelae,[64] although the findings of abnormal nodal function were not consistent with the presence of coronary stenosis/occlusion, and are believed to result from myocarditis or abnormal microcircu-

Table 11. Detection of Cardiac Complications by Common Physiological Examinations

Investigators	Examination	Target disease	Criteria	N	Sensitivity	Specificity
Osada M, et al[80]	QT dispersion	Coronary artery lesions	QT≥60 ms	56	100% (6/6)	92%
		Inferior wall infarction	deep Q in II, III, aVF	7	86%	97%
Nakanishi T, et al[59]	12-lead ECG	Anterior wall infarction	deep wide Q in V1-6	8	75%	99%
		Lateral wall infarction	deep Q in I, aVL	7	57%	100%
Ogawa S, et al[81]	Signal-averaged ECG	Myocardial ischemia	LP positive	198	69.2%	93.5%
Genma Y, et al[82]	Dobutamine stress signal-averaged ECG	Myocardial ischemia	LP positive	85	87.5%	94.2%
Takechi N, et al[83]	Dobutamine stress body surface potential mapping	Myocardial ischemia	nST>1	115	94.1%	98.9%
			I map≤4	115	41.7%	96.9%

LP, late potential; nST, non-stress test; I map, isopotential map.

lation in the conducting system.

(4) Signal-Averaged ECG

Signal-averaged ECG is believed to feature a better rate of detection of myocarditis associated with Kawasaki disease than standard 12-lead ECG, Holter ECG, echocardiography, and blood tests for cardiac enzymes.[65] Positive ventricular late potential adjusted for body surface area is highly specific for the detection of ischemia and chronic myocardial infarction,[66] and dobutamine stress tests may improve specificity further in children who cannot tolerate exercise testing.

4 Summary of Physiological Examinations

Table 11 summarizes the physiological examinations commonly used for patients with Kawasaki disease and their rates of detection of cardiac complications.

3. Diagnostic Imaging

1 Chest X Ray

(1) X-Ray Finding of Calcified Coronary Aneurysms

Since the presence of calcification of coronary aneurysms on chest X-ray suggests the presence or progression of giant aneurysms or stenotic lesions, CAG using MDCT or selective CAG is required.[67,68]

(2) Enlarged Heart Shadow due to Myocardial Ischemia or Valvular Diseases

An enlarged heart shadow is observed in patients with poor cardiac function due to chronic myocardial infarction, and in patients with volume overload caused by mitral or aortic insufficiency.

2 Echocardiography

(1) Echocardiography at Rest

Echocardiography at rest is the most commonly performed test, because it is non-invasive and convenient, and can be used to evaluate coronary morphology over time to detect coronary dilatations specific to the coronary artery lesions associated with Kawasaki disease.[69,70] Adults may be diagnosed with Kawasaki disease based on the visualizing of coronary aneurysms.[71] The presence/absence of thrombi within aneurysms can also be determined with echocardiography.[72] Although it is sometimes difficult to evaluate stenotic lesions with echocardiography,[73,74] it has been reported that following the improvement of ultrasonic device, measurement of coronary blood flow with Doppler echocardiography enables accurate diagnosis of stenotic lesions. It has also been reported that 3-dimensional (3D) echocardiography is useful in visualizing the right coronary artery and the circumflex artery, and in visualizing mural thrombi in coronary aneurysms. This technique is expected to become useful for the diagnosis of coronary artery lesions due to Kawasaki disease. Echocardiography is the most useful method for evaluation of deterioration of cardiac function due to myocardial injury and the severity of valvular disease.[75] Detailed reports have been published on evaluation of myocardial injury during the acute phase using tissue Doppler imaging.[76]

(2) Stress Echocardiography

Stress echocardiography is a method enabling real-time evaluation of left ventricular wall motion in patients during exercise (treadmill or ergometer)[77] or with administration of dobutamine[78] or dipyridamole.[79] Dobutamine stress echocardiography is particularly useful for detecting coronary stenotic lesions and evaluating the viability of myocardium. In dobutamine stress echocardiography, dobutamine is administered in incremental doses, which are increased by 5 to 10 μg/kg/min every 5 minutes to a highest dose of 30 to 40 μg/kg/min to check visually for abnormal wall motion in each slice.

(3) Others

Transesophageal echocardiography (TEE) may be useful in visualizing coronary arteries in adults suspected to have coronary aneurysms which are difficult to evaluate using transthoracic echocardiography.[84] It also may be used to evaluate coronary blood flow. Myocardial contrast echocardiography, the use of which has advanced through the widespread use of intravenous myocardial contrast echocardiography and the improvement of ultrasonic device, is now able to provide evaluation equivalent to that by myocardial scintigraphy and is expected to prove useful in the future because of its convenience.[85]

3 Radionuclide Imaging

Myocardial perfusion imaging techniques available for patients with Kawasaki disease include Planar and single photon emission computed tomography (SPECT), the latter of which is more commonly used. Thallium (^{201}Tl) is often used, and technetium (Tc)-labeled myocardial perfusion agents (Tc-99m sestamibi, Tc-99m tetrofosmin) which are low in radioactive exposure and suitable for scintigraphy are also commonly used.[86,87] Stress myocardial SPECT is an important method of diagnosis of coronary stenotic lesions after Kawasaki disease, and both exercise stress SPECT and pharmacological stress SPECT are commonly performed.[88–93] In addition to myocardial perfusion imaging techniques,

evaluation of myocardial fatty acid metabolism with ^{123}I β-methyl-p-iodophenyl-pentadecanoic acid (^{123}I BMIPP)[94] and evaluation of cardiac sympathetic nerve activity with ^{123}I metaiodobenzylguanidine (^{123}I MIBG)[95] are also used in the clinical setting. Ga-67 myocardial scintigraphy is useful in the diagnosis of myocarditis due to Kawasaki disease.[20]

(1) ^{201}Tl Myocardial Perfusion Scintigraphy

Lesions of myocardial ischemia may be located by obtaining stress images under administration of ^{201}Tl and then obtaining delayed images to investigate redistribution in areas with poor perfusion. Redistribution images are considered especially useful in predicting cardiac events due to coronary artery lesions associated with Kawasaki disease.[89] Specifically, ^{201}Tl is administered during stress at 37 MBq (1 mCi) in infants under one year of age, 37 to 56 MBq (1 to 1.5 mCi) in children 1 to 10 years of age, and 56 to 74 MBq (1.5 to 2 mCi) in children ≥10 years of age, and delayed images (redistribution images) are obtained 3 to 4 hours after administration of ^{201}Tl.[96] To obtain clear images, physicians should (1) exercise special caution in avoiding body movement by children during imaging, (2) obtain stress images promptly after administration of ^{201}Tl, since redistribution of ^{201}Tl occurs within a short period of time, and (3) ensure that patients do not eat from administration of ^{201}Tl until the time of delayed imaging.

(2) Tc-Labeled Myocardial Perfusion Scintigraphy

Tc-labeled myocardial perfusion agents such as Tc-99m sestamibi and Tc-99m tetrofosmin have been developed as alternatives to ^{201}Tl for use in myocardial perfusion imaging. These agents allow high-resolution, low-exposure imaging because of their short half-life. Once absorbed into the myocardium, Tc-labeled myocardial perfusion agents remain in the myocardium for a long period of time and are not redistributed, as occurs with ^{201}Tl. Images can thus be obtained regardless of time after administration, though images at rest should be obtained separately. Tc-labeled myocardial perfusion scintigraphy is performed under stress at a dose of 10 MBq/kg (maximum 370 MBq, 10 mCi), and the second dose is administered 2 to 3 hours after the first administration at 2 to 3 times the first dose (maximum 740 MBq, 20 mCi).[97] To obtain clear images, physicians should (1) exercise special caution in avoiding body movement by children during imaging, (2) continue stress for at least one minute after administration of perfusion agents under stress, (3) promote elimination of perfusion agents from the liver and gallbladder by ingestion of egg products, milk or cocoa, and (4) obtain images at least 30 minutes after administration of perfusion agents to ensure elimination of perfusion agents accumulated in the liver.

(3) ECG-Gated Myocardial Perfusion SPECT

The availability of 3D automatic quantitative analysis of ECG-gated myocardial perfusion SPECT (quantitative gated SPECT, QGS) has allowed physicians to calculate left ventricular volume and ejection fraction (EF) by evaluating wall motion and to visualize the endocardium based on multidimensional 3D images.[98] In patients with severe coronary artery lesions due to Kawasaki disease, detailed evaluation of postischemic myocardial stunning[99] and viability of infarcted myocardium may be performed with QGS,[100,101] though this method cannot be used effectively in patients with a small heart (diastolic volume of about ≤50 mL) under 6 years of age.

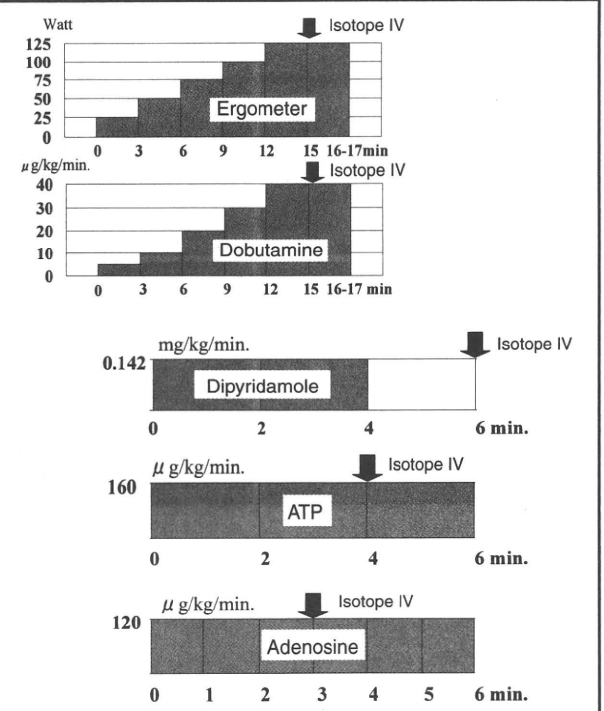

Figure 3. Administration of drugs during myocardial perfusion scintigraphy. IV, intravascular; ATP, adenosine triphosphate.

(4) Imaging of Myocardial Fatty Acid Metabolism

Imaging of myocardial fatty acid metabolism using ^{123}I BMIPP is a better technique for specification of segments with abnormal wall motion than myocardial perfusion imaging because it can specify abnormal energy production in the myocardium. Since areas with low myocardial uptake of ^{123}I BMIPP are strongly consistent with segments perfused by the culprit coronary vessel in patients with myocardial infarction or angina, this technique can be used in the evaluation of myocardial injury in patients with severe coronary artery lesions due to Kawasaki disease.[94]

(5) Imaging of Cardiac Sympathetic Nerve Activity

Imaging of cardiac sympathetic nerve activity can be obtained with ^{123}I MIBG imaging. Since abnormal cardiac sympathetic nerve activity follows the development of severe myocardial ischemia or myocardial infarction, ^{123}I MIBG imaging in patients suspected of having cardiac events including infarction may allow physicians to specify culprit vessel(s) promptly, and is thus quite useful in patients with coronary artery lesions due to Kawasaki disease who often experience asymptomatic myocardial ischemia.[95,102]

(6) Positron Emission Tomography (PET)

Quantitative evaluation of myocardial flow reserve can be performed in the evaluation of blood flow by PET using [O-15]-water or [N-13]-ammonia. Low myocardial flow reserve and poor vascular endothelial function have been observed in patients with regression of coronary aneurysms. Evaluation of glucose metabolism in PET using [F-18]-fluorodeoxyglucose (FDG) permits precise evaluation of the viability of infarcted myocardium.[103,104]

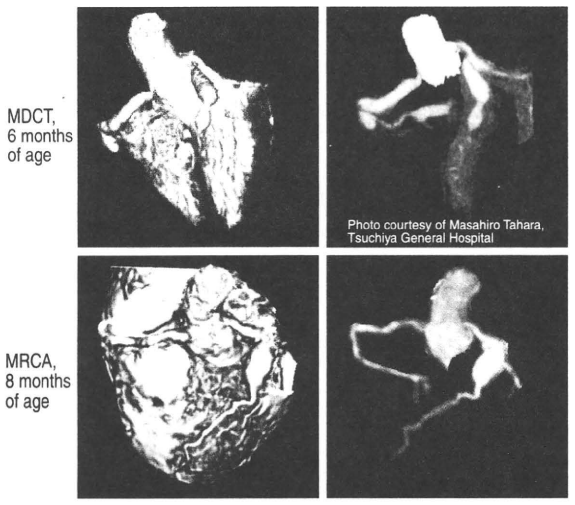

Figure 4. 64-row MDCT and MRCA in infants. MDCT, multi-row detector computed tomography; MRCA, magnetic resonance coronary angiography.

(7) Administration of Drugs During Myocardial Perfusion Scintigraphy

Figure 3 illustrates how drugs are administered during pharmacological myocardial perfusion scintigraphy.

4 Magnetic Resonance Coronary Angiography (MRCA) and MDCT

Selective CAG has been considered a gold standard for the diagnosis of coronary artery lesions due to Kawasaki disease, and IVUS has been used concomitantly to observe for thrombi in aneurysms and intimal hyperplasia. Recently, MDCT and coronary artery imaging using MRI (MRCA) have been developed, and are increasingly used to obtain additional findings supportive of those of CAG.

(1) MDCT

Although it has been believed that MDCT is not feasible in children because of the extensive X-ray exposure associated with it, use of contrast media, administration of β-blockers to slow heart rate, and the need for breath-holding, recent reports have indicated that 64-row MDCT provides clear images in young children who do not hold their breath during imaging[38] and do not undergo induction of slow heart rate, and may overcome the problems regarding breath and heart rate control when used more widely in the future (**Figure 4**).

(2) MRCA

MRCA is a completely non-invasive imaging technique which requires neither X-ray exposure nor contrast media. Since MRCA can be performed during spontaneous breathing without slowing of the heart rate, infants and young children may undergo it during sleep.[105]

There are two imaging techniques of MRCA, the bright blood technique [steady-state free precession (SSFP)] which indicates blood flow as white, and the black blood technique, which indicates blood flow as black and occlusions and intimal hyperplasia as gray (**Figure 4**). The black blood technique includes M2D black blood turbo spin echo imaging and 2D Black blood Spiral k-space order TFE technique (indicates coronary transection) which allows physicians to observe for thrombi and intimal hyperplasia.[106,107]

Although the rate of visualization of stenotic lesions is lower with MRCA than MDCT,[108,109] MRCA is more useful in visualization of localized stenosis with calcification because it does not hinder visualization of vascular lumens.[36,110]

(3) Magnetic Resonance (MR) Myocardial Imaging

MR myocardial imaging, which may be performed in a short time following MRCA, is a less expensive imaging technique without the need for radioisotopes, and may provide clearer 3D images than MRCA.

Cine MRI is performed using SSFP without contrast media to acquire images from the left ventricular short axis view, long axis view, and four-chamber view to observe ventricular wall motion, and perfusion MRI is performed after infusion of gadolinium-based contrast media to evaluate the severity of myocardial ischemia by observing the first pass of contrast media in the myocardium during adenosine triphosphate (ATP) stress and at rest from the left ventricular short axis view.[111]

Delayed-contrast enhanced MRI can visualize the extent and depth of subendocardial infarct lesions by obtaining images 15 minutes after the administration of contrast media with a sequence using T1-weighted gradient echo with myocardial T1 signal suppression. This technique can visualize subendocardial infarct lesions and small infarct lesions in the right ventricle, which cannot be visualized with radioisotope myocardial imaging. Since the prevalences of occlusions and recanalization of the right coronary artery are especially high in patients with Kawasaki disease, precise evaluation of the right ventricular myocardium is important.[112]

5 Cardiac Catheterization and CAG

(1) CAG

a) Indications

(1) Evaluation of Severity of Coronary Artery Lesions and Patient Follow-up

Although in the case of adults CAG is indicated for those who exhibit findings of myocardial ischemia, it is recommended for patients with Kawasaki disease that CAG should be performed in those with medium or giant aneurysms during the convalescence phase or later to monitor for the development or progression of localized stenosis, since myocardial ischemia due to Kawasaki disease cannot be fully detected with other types of examinations and myocardial ischemia may manifest as sudden death.[16]

(2) Percutaneous Coronary Intervention (PCI) Before and After Coronary Artery Bypass Grafting (CABG)

CAG is required before PCI to determine whether PCI is indicated, during angioplasty to ensure safe and effective intervention, and after angioplasty to evaluate the results of PCI and follow up patients.[90,113]

(3) Intracoronary Thrombolysis (ICT)

Thrombi in coronary aneurysms may sometimes be observed during follow-up of medium to giant aneurysms with echocardiography. In such cases, cardiac catheterization and CAG are performed for ICT.

b) Coronary Artery Lesions Indicated for CAG

(1) Dilatation Lesions

In patients with aneurysms classified as medium or giant according to the severity classification of cardiovascular lesions in the present guidelines, it is desirable to perform CAG during the early part of the convalescence phase for detailed evaluation of the morphology and extent of coronary artery lesions and to specify the methods and duration of follow-up and treatment strategies. Since precise evaluation of coronary stenotic lesions is feasible with MRCA and MDCT, it is expected that in the future it will be possible to omit catheterization for the diagnosis of coronary stenotic lesions in some patients.[105] Since the development of stenosis after regression of not only large aneurysms but also smaller ones[12] and the development of arteriosclerotic degeneration[14] have been observed in patients over 10 years after the onset of Kawasaki disease, patients should be followed for a long period of time using coronary imaging techniques such as MRCA and MDCT if follow-up CAG is not feasible.

(2) Localized Stenosis

During the remote phase, progressive localized stenosis develop mainly in the inlet and outlet of aneurysms. Multidirectional imaging is required to evaluate stenotic lesions. A significant stenosis is defined as a ≥75% stenosis in lumen diameter in the major coronary arteries and a ≥50% stenosis in lumen diameter in the left main coronary trunk. Patients with significant stenosis should be followed with angiography[16] or other imaging techniques such as MRCA[105] and MDCT[114] at appropriate intervals based on the speed of progression of the stenosis (from 6 months to several years), even when no signs/symptoms of myocardial ischemia are present, and should be considered for aggressive treatment such as CABG[113] and PCI[90] based on the results of the above-described follow-up imaging as well as the results of other studies such as myocardial scintigraphy, exercise ECG, and evaluation of coronary flow reserve (CFR).

(3) Occlusion

Complete occlusion of a coronary artery is observed in about 16% of patients with coronary artery lesion due to Kawasaki disease, and 78% of occlusions are visualized with imaging within 2 years after the onset of Kawasaki disease.[16] The finding of occlusion of the coronary arteries in asymptomatic patients on routine follow-up imaging is not uncommon. Collateral flows are visualized during angiography in all patients with coronary occlusion. Since the extent of collateral flow and growth/development of recanalized vessels differ among individuals and depend on the time after occlusion and cause of occlusion (thrombi vs intimal hyperplasia), follow-up angiography is required.[17]

(2) Cardiac Function Test

Cardiac function is evaluated by determining ventricular pressure, cardiac output, ventricular volume, EF, and/or other parameters.

(3) IVUS

a) Morphological Evaluation of Coronary Artery Lesions

IVUS is used to evaluate the severity of intimal hyperplasia, presence/absence of thrombi or calcification, and the severity of luminal narrowing. Severe intimal hyperplasia is observed not only in lesions of localized stenosis but also in

Table 12. Indications of Imaging Techniques by Classification of Severity of Coronary lesions Due to Kawasaki Disease

• **Chest X ray**		
▷Class I	Severity classification	III, IV, V
▷Class II	Severity classification	I, II
▷Class III	None	
• **Echocardiography/12-lead ECG at rest**		
▷Class I	Severity classification	I, II, III, IV, V
▷Class II	None	
▷Class III	None	
• **Exercise ECG**		
▷Class I	Severity classification	III, IV, V
▷Class II	Severity classification	I, II
▷Class III	None	
• **Holter ECG, signal-averaged ECG**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Body surface mapping, drug stress ECG, magnetocardiography**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Stress echocardiography, myocardial contrast echocardiography**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Myocardial perfusion scintigraphy**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **Evaluation of myocardial fatty acid metabolism, evaluation of cardiac sympathetic nerve activity**		
▷Class I	Severity classification	V
▷Class II	Severity classification	I, II, III, IV
▷Class III	None	
• **MRI, MDCT**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	I, II, III
▷Class III	None	
• **PET**		
▷Class I	Severity classification	V (b)
▷Class II	Severity classification	I, II, III, IV, V(a)
▷Class III	None	
• **Cardiac catheterization**		
▷Class I	Severity classification	IV, V
▷Class II	Severity classification	III
▷Class III	Severity classification	I, II

MRI, magnetic resonance imaging; MDCT, multi-row detector computed tomography; PET, positron emission tomography.

Class I	Conditions for which there is general agreement that the procedure is useful and effective.
Class II	Conditions for which there is a divergence of opinion regarding the usefulness/efficacy of a procedure.
Class III	Conditions for which there is general agreement that the procedure is not useful/effective and may in some cases be harmful.

Table 13. Performance of Common Imaging Techniques (Not Including Cardiac Catheterization)

Investigator	Technique	Stress	N	Sensitivity	Specificity
Hiraishi S, et al[73]	Transthoracic echocardiography Diagnosis of stenotic lesions	At rest	18	RCA: 85%, LAD: 80%	RCA: 98%, LAD: 97%
Noto N, et al[78]	Stress echocardiography Diagnosis of stenotic lesions	Dobutamine	26	90%	100%
Kondo C, et al[88]	^{201}Tl Diagnosis of stenotic lesions	Dipyridamole	34	88%	93%
Karasawa K, et al[124]	^{201}Tl Diagnosis of stenotic lesions	Dobutamine	24	71%	95%
Karasawa K, et al[124]	^{201}Tl Diagnosis of stenotic lesions	ATP	24	83%	92%
Karasawa K, et al[124]	Tc-99m tetrofosmin Diagnosis of stenotic lesions	Exercise, ATP, Dobutamine	20	90%	85%
Fukuda T, et al[125]	Tc-99m tetrofosmin Diagnosis of stenotic lesions	Dipyridamole	86	90%	100%
Hoshina M, et al[94]	^{123}I BMIPP Diagnosis of stenotic lesions	At rest	10	90%	73.9%
Kanamaru H, et al[114]	MDCT Diagnosis of stenotic lesions*	At rest	16	87.5% (25 vessels)	92.5% (52 vessels)
Miyagawa M, et al[89]	^{201}Tl Prediction of cardiac events	Dipyridamole	15	93%	83%
Suzuki A, et al[36]	MRCA Diagnosis of stenotic lesions**	At rest	70	occlusion 94.2%, stenosis 94.4%	occlusion 99.5%, stenosis 97.2%

*Of 80 vessels in 16 patients with coronary lesions, 77 vessels could be evaluated with MDCT.
**Among 70 patients with coronary lesions, evaluation was performed in 210 vessels of patients with occlusion and 54 vessels of 18 patients with regional stenosis.
Tl, thallium; Tc, technetium; BMIPP, β-methyl-p-iodophenyl-pentadecanoic acid; MDCT, multi-row detector computed tomography; MRCA, magnetic resonance coronary angiography; ATP, adenosine triphosphate; RCA, right coronary artery; LAD, left anterior descending coronary artery.

aneurysms that have regressed. Intimal narrowing and calcification, not detected with angiography may be visualized with IVUS. It has been found that obvious intimal hyperplasia may develop during the remote phase in aneurysms with an internal diameter during the acute phase of >4 mm.[19] Evaluation of lesions, and especially quantitative evaluation of calcified lesions with IVUS, is required when the means to be used for PCI are selected.[28]

b) Coronary Arterial Vasodilator Function

It has been reported that the absence of coronary vasodilatation in coronary artery wall following administration of isosorbide dinitrate (ISDN) or acetylcholine suggests the presence of chronic intimal dysfunction in patients with Kawasaki disease.[27,115] However, since evaluation of coronary arterial vasodilator function may induce coronary spasm or other adverse reactions, its potential benefits and risks should be carefully weighed before it is performed.

c) PCI

Preoperative examination should be performed to determine the severity of stenosis and its calcification and the condition of the intima in detail in order to select appropriate means for the performance of PCI. IVUS should be performed in every step of PCI to ensure the safety and efficacy of treatment. IVUS is also useful in the evaluation of postoperative restenosis.[28,116]

(4) Functional Severity Evaluation Using Flow Wires or Pressure Wires

Determination of average peak flow velocity (APV), CFR, and myocardial fractional flow reserve (FFRmyo) using a 0.014-inch guidewire equipped with an ultrasonic probe and a high-sensitivity pressure sensor (Doppler wires or pressure wires) is useful in evaluation of the functional severity of coronary artery lesion in patients with coronary artery lesions due to Kawasaki disease. CFR (CFR=[stress APV]/[APV at rest], where APV is the value at peak dilatation after infusion of papaverine hydrochloride injection) and FFRmyo (FFRmyo=[Mean pressure at a site distal to the coronary lesion of interest]−{[mean right atrial pressure]/[mean pressure at the coronary ostium]}−[mean right atrial pressure]), where these pressures are obtained simultaneously at peak dilatation after infusion of papaverine hydrochloride) are particularly suitable for the evaluation of the presence/absence and severity of myocardial ischemia and presence/absence of peripheral coronary circulatory disorder. These values are also useful in selecting appropriate treatment strategies (catheter intervention vs CABG) and postoperative evaluation. Measurements obtained with pressure wires are useful in the evaluation of stenotic lesions, and those with Doppler wires in the evaluation of dilatation lesions.[117]

The reference values in children are 2.0 for CFR and 0.75[117] for FFRmyo, and identical to those in adults.[118–121]

4. Summary of Examinations

As **Table 12** shows, appropriate imaging techniques should be selected based on the severity of coronary artery lesions. **Table 13** lists the diagnostic performance of the imaging techniques mainly used in the evaluation of cardiovascular sequelae in Kawasaki disease.

Selection of treatment strategies for cardiovascular sequelae in Kawasaki disease must be made on the basis of careful consideration of the pathological condition of each patient and the results of comprehensive multimodal analysis of findings obtained with different imaging techniques.

Table 14. Guidelines for Treatment of Patients With Persistent Coronary Aneurysms/Dilatation During the Chronic Phase

I Patients without angina or detectable ischemia	
• Combination therapy using antiplatelet drugs	
° Examination revealed obvious ischemia	Antiplatelet drugs + Ca-blockers
II Patients with angina	
• In addition to combination therapy using antiplatelet drugs	
° Angina on exertion	Nitrates, monotherapy or combination therapy of Ca-blockers, plus β-blockers if ineffective
° Angina at rest or during sleep	Ca-blockers
° Angina at night	Ca-blockers + nitrates or K-channel openers (nicorandil)
III Patients complicated by cardiac dysfunction or valvular disease	
• Severity of cardiac dysfunction should be evaluated appropriately. Monotherapy or combination therapy using β-blockers, ACE inhibitors, angiotensin II receptor blockers, or statins should be added to antianginal drugs.	

ACE, angiotensin converting enzyme.

Table 15. Antiplatelet Drugs and Anticoagulant Drugs

Drug	Dose	Adverse drug reactions (ADRs) and precautions
Acetylsalicylic acid (Bufferin or Bayaspirin)	30 to 50 mg/kg divided into 3 doses during the acute phase, 3 to 5 mg/kg once daily after defervescence	Hepatic function disorder, gastrointestinal ulcer, Reye syndrome (higher incidence at ≥40 mg/kg), bronchial asthma Use other drugs during varicellainfection and influenza.
Flurbiprofen (Froben)	3 to 5 mg/kg, divided into 3 doses	Hepatic function disorder, gastrointestinal ulcer Use when severe hepatic disorder due to aspirin develops.
Dipyridamole (Persantin, Anginal)	2 to 5 mg/kg, divided into 3 doses	May induce angina in patients with severe coronary stenosis. Coronary steal phenomenon, headache, dizziness, thrombocytopenia, hypersensitivity, dyspepsia
Ticlopidine (Panaldine)	5 to 7 mg/kg, divided into 2 doses	Thrombotic thrombocytopenic purpura (TTP), leukopenia (granulocytopenia), serious hepatic function disorder Blood tests must be performed every other week during the first 2 months of treatment.
Clopidogrel (Plavix)	1 mg/kg, once daily	TTP, gastrointestinal symptoms, malaise, myalgia, headache, rash, purpura, pruritus Bleeding tendency may develop when used with aspirin.
Unfractionated heparin (IV) Low-molecular-weight heparin (SC)	Loading dose 50 units/kg, maintenance dose 20 units/kg to maintain an APTT of 60 to 85 sec (1.5 to 2.5 times baseline) • Infants <12 months of age Treatment: 3 mg/kg/day, divided into 2 doses (every 12 hours) Prevention: 1.5 mg/kg/day, as above • Children/adolescents Treatment: 2 mg/kg/day, divided into 2 doses (every 12 hours) Prevention: 1 mg/kg/day, as above	Major ADRs: Shock/anaphylactoid reaction, bleeding, thrombocytopenia, thrombocytopenia/thrombosis associated with heparin-induced thrombocytopenia (HIT)
Warfarin (Warfarin)	0.05 to 0.12 mg/kg, once daily (0.05 to 0.34 mg/kg/day in the AHA guidelines) 3 to 7 days required to obtain efficacy	Dose should be adjusted to an INR of 1.6 to 2.5 (2.0 to 2.5 in the AHA guidelines) and a thrombotest (TT) value of 10 to 25%. Sensitivity to this drug, hepatic function disorder, and bleeding ADRs are possible. The effect of warfarin may be reduced by barbiturates, steroids, rifampicin, bosentan hydrate, and vitamin K-rich foods such as natto, spinach, green vegetables, chlorella, and green juices. The effect of warfarin may be increased by chloral hydrate, NSAIDs, amiodarone, statins, clopidogrel, ticlopidine, antitumor drugs, antibiotics, and antifungal drugs.

The safety and efficacy of the above drugs have not been established in children.
IV, intravenous; SC, subcutaneous; APTT, activated partial thromboplastin time; AHA, American Heart Association; INR, international normalized ratio; NSAIDs, nonsteroidal antiinflammatory drugs.

IV Treatment Methods

1. Pharmacotherapy

1 Treatment Policy

In assessment of cases of death during the remote phase in patients complicated by coronary artery lesion, the major cause of death has been found to be ischemic heart disease due to stenotic lesions resulting from coronary intimal hyperplasia or thrombotic occlusion.[122,123] In general, treatment of myocardial ischemia is performed to:

- Increase coronary blood flow
- Prevent or relieve coronary spasm
- Inhibit the formation of thrombi
- Decrease cardiac work

Accordingly, vessel wall remodeling and myocardial protection are the principal purposes of treatment.[126]

2 Treatment of Ischemic Attacks

(1) Treatment During Attacks

Sublingual administration of tablets of nitroglycerin, a fast-acting nitrate, is commonly performed to treat attacks of stable angina. Attacks will subside in 1 to 2 minutes in patients responding to sublingual nitroglycerin, while patients not responding to it should take additional sublingual tablets 5 to 10 minutes later. Since the standard dose for children has not been established, nitroglycerin should be administered at a dose calculated from the standard dose in adults.

(2) Prevention of Development of Angina Pectoris

Table 14 summarizes treatment policies for patients who still have coronary aneurysm or dilatation during the chronic phase.

(3) Prevention of Development (and Recurrence) of AMI

Among those with AMI complicated by coronary artery lesions due to Kawasaki disease, AMI occurred during sleep or at rest in 63% of patients and was not closely associated with physical activity and exertion.[127] In addition, asymptomatic AMI occurred in 37% of the patients. Pharmacotherapy for AMI should be designed to prevent the progression of intimal hypertrophy to stenotic lesions and inhibit the formation of thrombi, considering the poor myocardial oxygen consumption that may be present and possible involvement of coronary spasm in the development of myocardial infarction.

3 Pharmacotherapy

(1) Antiplatelet drugs (Table 15)

Platelet count decreases slightly immediately after the onset of Kawasaki disease (acute phase), and increases during the convalescence phase. Since platelet aggregation activity remains high during the first 3 months after onset and in some cases the first several months to 1 year after onset, it is preferable that patients with Kawasaki disease, including those without coronary sequelae, should be treated with antiplatelet drugs at low doses for about 3 months.[128–130]

On the other hand, patients with coronary aneurysm due to Kawasaki disease should receive antiplatelet drugs continuously to prevent ischemic heart disease and prevent the formation or growth of thrombi by platelet activation.

(2) Anticoagulant Drugs (Table 15)

Treatment with anticoagulant drugs is indicated for patients with medium or giant coronary aneurysms, patients with a history of AMI, and patients with abrupt dilatation of a coronary artery associated with a thrombus-like echo, among others. Patients with thrombi in coronary aneurysms should be treated with warfarin or heparin. Combined use of aspirin and warfarin is needed to prevent thromboembolism in patients with giant coronary aneurysms.[131,132] Patients should be carefully monitored for bleeding tendency due to excessive anticoagulant therapy. Children exhibit considerable individual differences in responses to anticoagulant therapy.

(3) Coronary Vasodilators and Antianginal Drugs (Table 16)

a) Ca-Blockers

In patients with Kawasaki disease, myocardial infarction may occur at rest or during sleep. Addition of Ca-blockers to the existing regimen should be considered for patients complicated by coronary spasm[133,134] and patients with post-infarct angina or myocardial ischemia.

b) β-Blockers

Among patients with Kawasaki disease, β-blockers may be administered to prevent reinfarction or sudden death in those with a history of myocardial infarction and to decrease long-term mortality. However, treatment with β-blockers may exacerbate already-existing coronary spasm.

β-blockers exerts antianginal effects by decreasing myocardial oxygen consumption.

c) Nitrates

Although the coronary vasodilatative effects of nitrates are not expected to be beneficial in the treatment of acute ischemia due to lesions with poor endothelial sell function, nitrates in sublingual or oral spray form should be attempted in treating AMI.[135,136]

(4) Drugs for Heart Failure (Table 16)

Angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs)

ACE inhibitors and ARBs may be administered to patients with left ventricular dysfunction (EF ≤40%) following myocardial infarction due to ischemic heart disease in order to decrease morbility, mortality, and the incidence of cardiac events. No study results have been published regarding the effects of ACE inhibitors and ARBs on the long-term prognosis of Kawasaki disease.

2. Non-Pharmacological Treatment

1 PCI

Unlike coronary lesions in adults, which are typically atherosclerotic lesions, the coronary lesions in patients with Kawasaki disease are often characterized by severe calcification and fibrous thickening. It is thus inappropriate and in some cases even dangerous to apply the indications for and procedures of PCI for adult patients to the treatment of patients