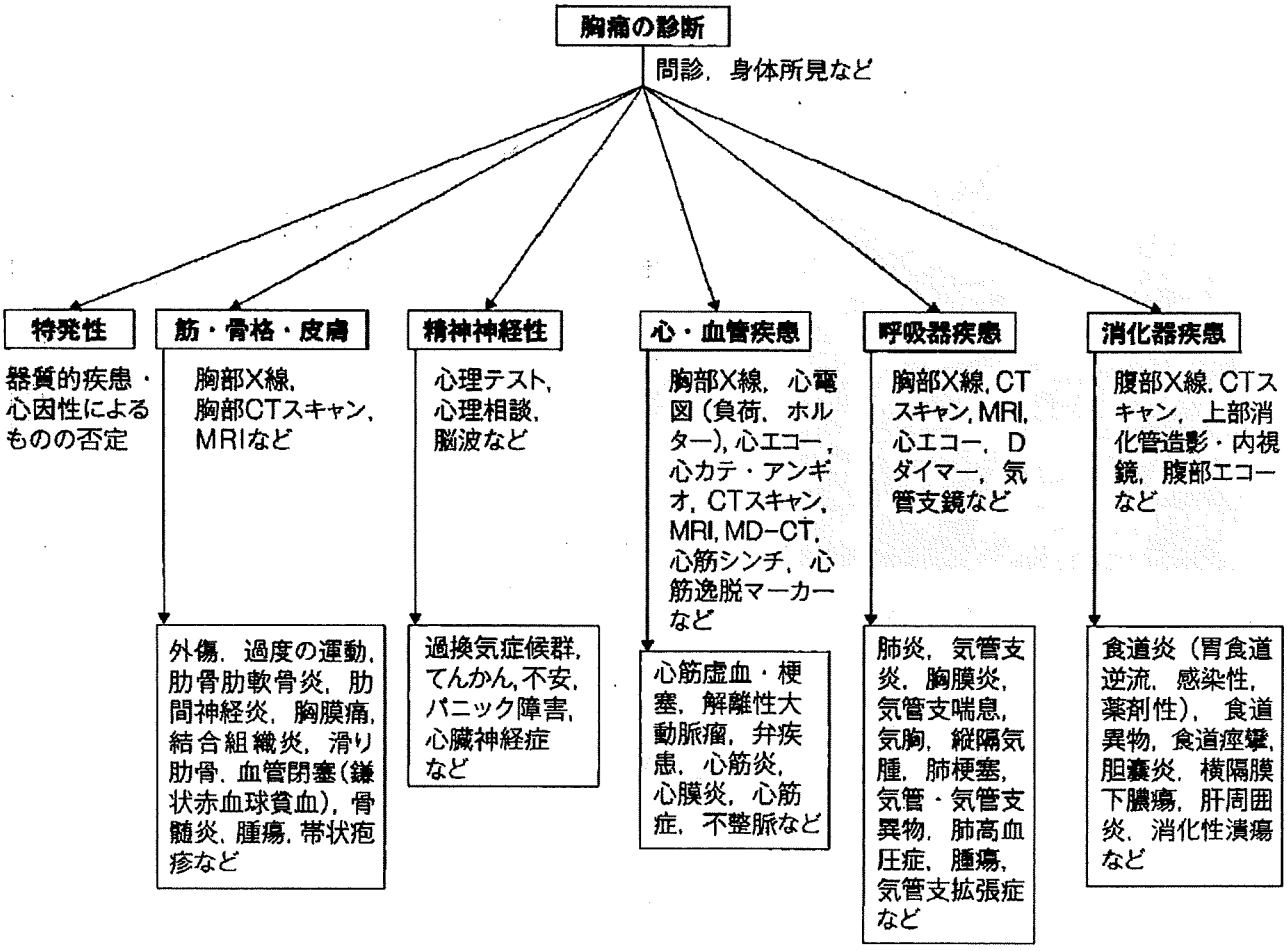


図2　胸痛を診断するためのフローチャート

える。ただし、反復することがあり、胸痛を受容することが必要であることも懇切丁寧に伝える。運動制限も必要ない。

(2)筋・骨格・皮膚

診断には胸部単純X線、CTスキャン、MRI検査が有用であることが多い。肋軟骨炎には非ステロイド系抗炎症薬の内服や貼付を、帯状疱疹では対症療法的に行われることが多いが、必要に応じてアシクロビルの内服を行う。

(3)精神神経性

心理テストなどを含む心理相談が必要である。小児科医ばかりでなく、必要に応じて小児精神神経科医の診断・治療を仰ぐことも必要な場合がある。

(4)心・血管疾患

心電図（負荷心電図、ホルター心電図を含む）、胸部単純X線、心エコー、ドップラー検査、心臓カテーテル・アンギオ検査が有用である。心膜炎ではCTスキャン、MRI検査が、また大血管疾患の診断には、それらに加えてMD-CT（multi-detector-row CT）スキャンが有用で、解離性大動脈瘤を疑った場合には造影CTスキャン、造影MRI検査を施行する。

心筋梗塞、心筋虚血や心筋疾患を疑った場合には核医学検査（心筋シンチ：^{201}Tl，^{99m}Tc MIBI，^{99m}Tc tetrofosmin，心筋脂肪酸代謝イメージング：^{123}I BMIPP，心筋交感神経機能イメージング：^{123}I MIBG）、血液生化学検査も重要である。特に、心筋梗塞の診断は一刻を争うものであり、心筋逸脱マーカーとしてトロップTセンシティブ（troponin T）検出のための迅速キット：V0・1 ng／mℓが陽性）、ラピチェック® H-FABP（heart-type fatty acid binding protein）検出のための迅速キット：V6・2 ng／mℓが陽性）による迅速診断は必須である[7]。

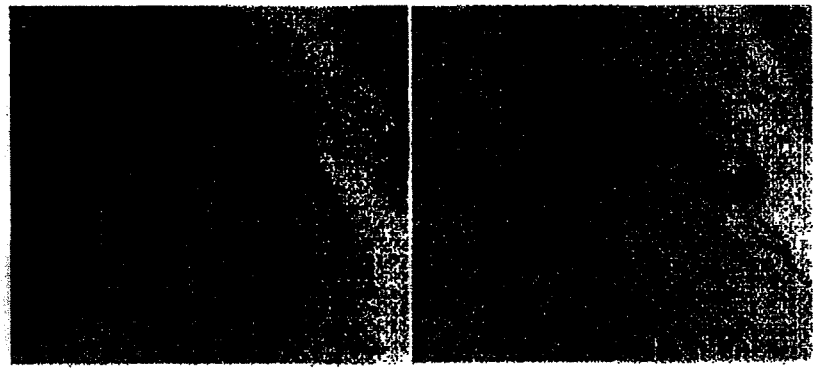
特発性僧帽弁逸脱症は治療の対象にならない。さらに、僧帽弁閉

鎖不全を伴わない特発性僧帽弁逸脱症の場合には定期的なフォローの必要もなく、学校生活管理指導表は「管理不要」でよい。

解離性大動脈瘤であれば緊急外科手術の適応となる。

急性心筋梗塞の治療の第一は再灌流による虚血解除であり、同時に心不全や不整脈などの急性心筋梗塞の合併症に対しての治療も行う。発症早期であれば、冠動脈造影や再灌流療法に備えて実施可能な施設に転送する。

小児において再灌流療法が適応となる多くのものが、川崎病後の冠動脈瘤の血栓性閉塞に起因するものであり(図3)、血栓溶解療法の臨床的意義は大きい。治療開始が早期であるほど、その治療効果が期待される。ACC(American College of Cardiology)／AHA(American Heart Association)ガイドラインでは、血栓溶解療法の適応は発症後12時間以内とされている。



安静時の左冠動脈造影　　急性心筋梗塞時の左冠動脈造影

図3　川崎病後に急性心筋梗塞を起こした男児例

5歳，男児．川崎病の病初期より両側に巨大冠動脈瘤が出現．安静時の左冠動脈造影では巨大な冠動脈瘤と遅延して造影される前下行枝，回旋枝が観察された．さらに，血管内エコー(IVUS)では壁在血栓が認められた．

その後，回旋枝の血栓閉塞による急性心筋梗塞を発症し，遠隔地であり再灌流療法を行うまでに約10時間要した．

入院時のPT/INRは2.1とよくコントロールされていた．t-PA(モンテプラーゼ)の冠動脈内注による再灌流療法に反応せず，大動脈内バルーンパンピング(IABP)を施行し，5日後に冠動脈バイパス術(左内胸動脈と前下行枝とのバイパス術)を施行．

心筋虚血の治療は、虚血を誘発する原因により異なるが、器質的な冠動脈狭窄によるものであれば、冠動脈インターベンション(PCI)を考慮する。安定狭心症の発作時にはニトログリセリン錠の舌下投与を、また、発症予防にはβ遮断薬やCa拮抗薬が有効である。

(5)呼吸器疾患

胸部単純X線検査が主体となる。その他CTスキャン、MRI検査も有用である。肺塞栓を疑った場合には、Dダイマーの測定、造影CTが有用であり、必要に応じて抗凝固療法を行う。また、呼吸器の炎症を疑った場合には、画像診断の他に血液・生化学検査が必須となる。

気管支喘息、気管支炎、肺炎に伴う胸痛の際には原疾患の治療を行う。胸膜炎に伴う多量の胸水の貯留が認められる場合には胸腔穿刺を行い、必要に応じて持続ドレナージを施行する。

気胸についても、胸腔内に溜まった空気の圧が高まり縦隔を対側に圧排するような緊張性気胸では、胸腔内穿刺を行い持続脱気する。

(6)消化器疾患

消化器疾患による胸痛を疑った場合の検査としては、まず腹部単純X線写真を撮る。その他、逆流性食道炎、潰瘍を疑った場合には上部消化管造影検査、内視鏡検査を、さらに肝・胆・膵の疾患を疑った場合には腹部超音波、腹部CTスキャンなどが有用である。診断を確定した後、的確な治療を行う必要がある。

□■□文　献□■□

1) Kocis KC : Pediat Clin North Am 46 : 189, 1999. 2) Bernstein D : Nelson Textbook of Pediatrics 17th Ed, WB Saunders, 2004, p1481. 3) Fukushige J, et al : Acta Paediatr Jpn 30 : 604, 1988. 4) Brown RT : J Adolesc Health Care 1 : 198, 1981. 5) Cava JR, et al : Pediatr Clin North Am 51 : 1553, 2004. 6) Anzai AK, et al : Am Fam Physician 53 : 1682, 1996. 7) Morrow DA, et al : Circulation 108 : 250, 2003.

Multicenter and Retrospective Case Study of Warfarin and Aspirin Combination Therapy in Patients With Giant Coronary Aneurysms Caused by Kawasaki Disease

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Background: To determine the prognosis of patients with giant coronary aneurysms (GA) caused by Kawasaki disease (KD) treated with combined oral warfarin and aspirin.
Methods and Results: A multicenter follow-up study of 83 patients (65 males, 18 females) with GA who had been treated for ≥3 months with warfarin. Most patients were placed on the combination therapy as soon as the GA was detected and remained on it for 6.0±5.3 years, giving a total of 482 patient-years. Target international normalized ratio of prothrombin time ranged from 1.5 to ≥2.5. During this observational period, 5 patients suffered from 8 episodes of acute myocardial infarction and 1 died. Coronary thrombus formation enforced 6 courses of intracoronary thrombolysis in 3 patients (1–4 times). Consequently, freedom of cardiac events was 92.5% at 1 year and 91% at 10 years and the linearized cardiac event rate was 2.9% patient-year. Hemorrhagic complications occurred on 8 occasions (1 subdural hematoma) in 5 patients, giving 1.7% patient-year.
Conclusions: The combination of warfarin and aspirin has an acceptably high cardiac-event-free survival in patients with GA caused by KD, though it has a certain risk of hemorrhagic complications. (*Circ J* 2009; **73:** 1319–1323)

Key Words: Anticoagulants; Antiplatelets; Coronary artery disease; Kawasaki disease; Prognosis

Kawasaki disease (KD) is the most frequent acquired cardiovascular disease in developed countries[1,2] Although intravenous gamma globulin infusion is the currently the recommended treatment, a certain number of patients still develop coronary aneurysms[1,2] which undergo senescence[3] leading to higher long-term mortality in male patients with KD[4] In particular, coronary aneurysms with diameter ≥8.0 mm are categorized as giant coronary aneurysms (GA) and are known to predispose to acute thrombotic occlusion, leading to acute myocardial infarction (AMI) and future stenosis, again leading to ischemic heart disease[5,6] Although the guidelines from the American Heart Association[7] and the Japanese Circulation Society[8] recommend aspirin with or without warfarin to prevent catastrophic cardiac events in KD patients with GA, the efficacy of anticoagulation therapy using warfarin has not been determined. On the other hand, anticoagulation treatment in an infant obviously carries significant risk of hemorrhagic complications[9–11]

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Part of this study was presented at the Annual Meeting of the American College of Cardiology 2007.
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As a general practice at Kurume University, we have administered warfarin in association with aspirin in patients with GA caused by KD since 1990 and have demonstrated that this combination therapy decreases the risk of myocardial infarction (5% vs 33%, P<0.05)[12] Conversely, Levy et al did not see any significant difference in the frequency of myocardial ischemic events between a small number of patients with GA treated with warfarin and those not given warfarin (13 vs 9)[13] Therefore, the aim of this multicenter study was to determine the outcome and complications of a large sample of patients with GA caused by KD who are treated with oral warfarin and aspirin.

Methods

Subjects of this study were patients with a history of KD and a GA ≥8 mm in diameter who had been placed on combination therapy of warfarin and 3–5 mg/kg (maximum 100 mg) of aspirin for ≥3 months. We sent questionnaires to the 6 participating institutions. The questions included date of birth; date of onset of KD; gender; location and maximum diameter of GA; starting date, duration, and reasons for maintaining or ceasing warfarin treatment; target, mean, lowest and highest international normalized ratio of prothrombin time (PT-INR) in each patient; additional medications; cardiac events before, during or after warfarin treatment and PT-INR before cardiac events; asymptomatic coronary occlusion; hemorrhagic complications; final outcome. The study protocol was approved by each institution's research committee. In this study, cardiac events were clinically diagnosed AMI and impending AMI treated by intracoronary thrombolysis (ICT), but did not

Table 1. Demographics of the Study Patients

Gender (M/F)	65/18
Age at onset of KD (years)	3.5±3.0 (range 0.2–14.5)
Location of giant aneurysm	Both LCA and RCA 48; isolated RCA 14; isolated LCA 21
Maximum diameter of aneurysm (mm)	Median 11 (range 8–39.5)
Age at start of Wa+ASA (years)	4.6±4.1 (range 0.2–17)
Duration of Wa+ASA (years)	5.8±5.2 (range 0.2–22.5)

KD, Kawasaki disease; LCA, left coronary artery; RCA, right coronary artery; Wa+ASA, combination of warfarin and aspirin.

Table 2. Profile of Anticoagulation Divided by Target PT-INR

Target PT-INR	No. of Patients	Mean PT-INR	Lowest PT-INR	Highest PT-INR	Mean interval of blood sampling (months)
1.5	5	1.4±0.3	1.0±0.1	2.0±0.8 (2.3)	1.5±0.9
1.5–2.0	24	1.5±0.3	1.1±0.1	2.7±1.2 (5.3)	3.3±3.2
2.0	24	1.9±0.4	1.4±0.2	3.1±0.8 (4.6)	1.9±0.8
2.0–2.5	11	2.1±0.2	1.6±0.1	3.2±0.6 (4.0)	2.1±0.3
–2.5	4	2.2±0.4	1.5±0.2	3.8±1.8 (6.4)	1.5±0.5

Values are mean and standard deviation in each patient group.
Because not all patients had sufficient data for the analysis, the number of patients in each group is different from the text.
The numbers in the parenthesis are the highest value in each group.
Note: the mean PT-INR is below the target PT-INR in all patients except those with target PT-INR of 2.0–2.5.
PT-INR, international normalized ratio of prothrombin time.

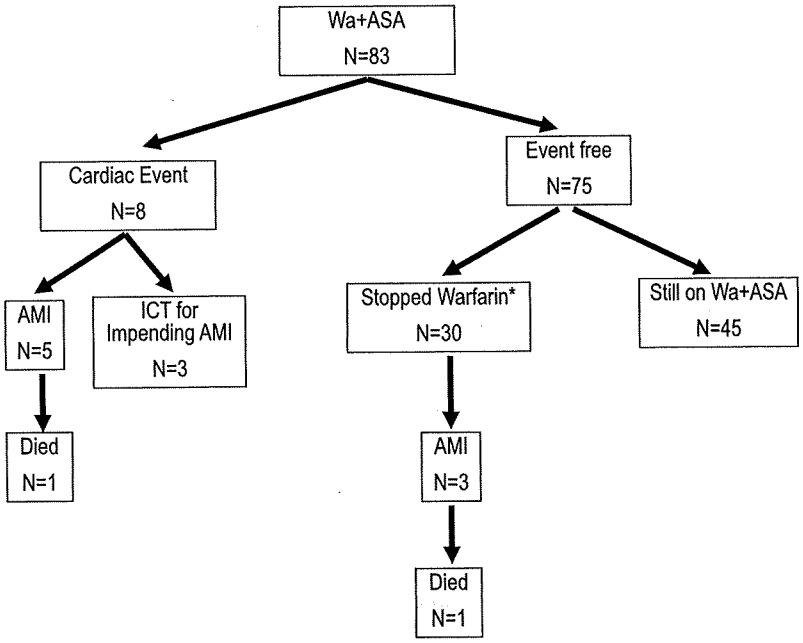

Figure 1. Outcome of patients with GA treated by combination therapy of warfarin and aspirin. *Wafarin was ceased because of successful CABG (15), regression of GA (8), occlusion of the GA (4), social reasons (2), and hemorrhagic complication (1). AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; GA, giant coronary aneurysms; ICT, intracoronary thrombolysis; Wa+ASA, combination of warfarin and aspirin.

include elective cardiac intervention for ischemic coronary artery disease.

Statistical Analysis

Based on the data, cardiac-event-free curves were generated using the Kaplan-Meier method, and frequencies of cardiac events and hemorrhagic complications were expressed as percent patient-year. In addition, mean and standard deviation of the mean, lowest and highest PT-INR in subgroups of patients divided by target PT-INR were calculated.

Results

Demographic data of the study patients are shown in **Table 1**. In most patients combination warfarin and aspirin therapy was started as soon as a GA were detected (>1 year after onset of KD in 12 patients) and administered for 5.8±5.2 years (range 0.2–22.5), giving a total of 482 patient-years. In 17 of 83 (20.5%) patients, combination therapy was administered for more than 10 years. Target PT-INR was 1.5 in 5, 1.5–2.0 in 31, 2.0 in 27, 2.0–2.5 in 11, ≥2.5 in 4 and not available in the remaining 5 patients. In patients who were monitored by Thrombotest®, the results were converted to PT-INR.[14] Actual mean and standard deviation of the mean, lowest, and highest PT-INR in the subgroups

Table 3. PT-INR Before AMI

Patient no.	CE	Age at onset of KD (years)	Interval from the onset to CE (months)	PT-INR before CE	Target PT-INR	Mean interval of blood sampling (months)	Actual mean, lowest, and highest PT-INR
1	AMI (3rd episode)	5.4	12	1.1	1.5–2.0	1	1.7 (1.0–3.9)
2	AMI	9.8	4	1.5	2.0	2.5	2.1 (1.5–3.6)
3	AMI	7.7	12	1.1	2.0	–	–
4	ICT (4th episode)	0.7	12	2.7	2.5	1	2.3 (1.1–4.9)
5	ICT	0.3	2	1.8	2.5	1	2.5 (1.2–6.4)
6	ICT	1.8	15	1.9	2.0	2.5	1.9 (1.5–3.4)

PT-INR was measured within 1 month of AMI.
AMI, acute myocardial infarction; CE, cardiac event; ICT, intracoronary thrombolysis. Other abbrebiations see in Tables 1,2.

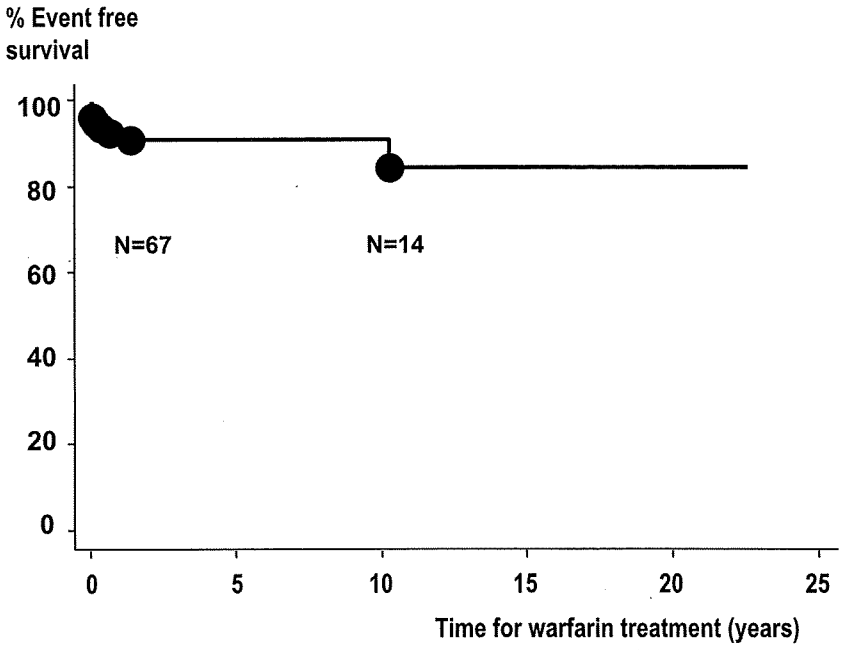

Figure 2. Cardiac-event-free survival in patients with giant coronary aneurysms treated by warfarin and aspirin.

of patients divided by target PT-INR are shown in **Table 2**.

Additional medications included dipyridamole in 34 (41%), ticropidine in 20 (24%), angiotensin II receptor blocker in 13 (16%), calcium-channel blocker in 6 (7%), bucolome in 5 (6%), β-blocker in 5 (6%), and angiotensin-converting enzyme inhibitor in 3 (4%) patients. Bucolome, a uricosuric agent, was added to intensify the anticoagulant effect of warfarin![13]

Among 83 patients, 5 (6%) with bilateral GA suffered from 8 episodes of AMI (**Figure 1**). Patient 1 (in **Table 3**) suffered from AMI 4 times at 1, 11, 12, and 14 months after the onset of KD and showed thrombus in the coronary artery at 5 months after the onset. He underwent successful ICT for the first 4 episodes, but for the last AMI he was medically treated only. Another patient showed thrombus in a GA at 2 months after the onset of KD and underwent successful thrombolysis with intravenous administration of tissue plasminogen activator, but died from AMI 2 months later. In the remaining 3 patients who suffered from AMI, 1 underwent successful ICT combined with balloon angioplasty at 4 months after KD onset (patient 2 in **Table 3**), and the other 2 showed signs and symptoms of AMI at 6 months and 10 years (patient 3 in **Table 3**) after onset, respectively, and both recovered with medical treatment only.

Another 3 patients (4%) with bilateral GA were found to have intracoronary thrombus in the GA at follow-up catheterization and underwent a total of 6 ICT procedures. Patient 4 (in **Table 3**) with an occluded left anterior descending artery underwent 4 ICT, 3 for thrombus in the left circumflex artery at 21, 30, and 35 days and 1 for thrombus in the right coronary artery (RCA) at 1 year after KD onset. The remaining 2 patients underwent ICT once each at 2 months (patient 5 in **Table 3**) and 1 year (patient 6 in **Table 3**) after onset, respectively. In 6 of 14 cardiac events, PT-INR was recorded before AMI and ranged between 1.1 and 2.7 (**Table 3**).

Combining the data, total cardiac events were 14, and 10 (88%) events occurred within 1 year after KD onset. In the whole group, freedom from cardiac events was 92.7% at 6 months, 92.7% at 1 year, 91.2% at 5 years, and 91.2% at 10 years after onset (**Figure 2**), and the linearized cardiac event rate was 2.9% patient-year.

Among 12 patients who did not take warfarin in the first 12 months, 5 patients had an AMI or underwent cardiac intervention before starting warfarin treatment. Among them, 3 patients had an AMI 1 year (2 patients), and 7 years (1 patient) after the onset, respectively; 1 underwent coronary artery bypass graft surgery (CABG) at 11 years after onset, and the other underwent percutaneous coronary balloon angioplasty at 14 years after onset. Even excluding

these 12 patients, freedom from acute cardiac events did not change significantly and was 91.5% at 1 year and 90% at 10 years. An additional 9 patients (16%) were found to have asymptomatic coronary artery occlusion, 6 in the RCA and 3 in the left coronary artery (LCA), at follow-up catheterization.

Cessation of Warfarin Treatment and Cardiac Events

Among 75 patients who did not have a cardiac event, 30 had ceased taking warfarin because of successful CABG (15), regression of GA (8), occlusion of the GA (4), social reasons (2) or hemorrhagic complication (1). Among those 30 patients, 3 patients suffered from AMI after ceasing warfarin treatment. A 21-year-old patient, who had bilateral GA of 34×68 mm in the LCA and 10 mm in the RCA and had been taking warfarin for 9 years without any cardiac events, ceased warfarin in preparation for scheduled CABG. Within 1 week, he collapsed suddenly because of AMI and could not be saved. Another 5-year-old patient, who had bilateral GA of 10 mm in the LCA and 9 mm in the RCA and had been taking warfarin for 4 years without any cardiac events, ceased warfarin when he entered kindergarten and suffered from AMI 6 months later. He was successfully treated and was on warfarin for more than 10 years since, until he underwent successful CABG. The remaining patient, who had bilateral GA of 10 mm in the RCA and 8.8 mm in the LCA and had been taking warfarin for 2.1 years without any cardiac events, ceased warfarin when coronary angiography showed partial regression of the GA. He suffered from AMI caused by occlusion of the RCA 2.7 years later, but was successfully treated and underwent successful CABG 1 month later.

Beside the 15 patients who underwent successful CABG and ceased warfarin, 5 patients who underwent CABG were still on warfarin at final follow-up of 0.8, 1.9, 3.9, 4.8, and 10 years after CABG because of developing stenosis in the remaining coronary arteries.

Hemorrhagic Complications and Withholding Warfarin

Hemorrhagic complications occurred on 8 occasions in 5 patients, giving a frequency of 1.7% patient-year. Among these, 6 episodes in 4 patients were associated with contusion. A 7-month-old-infant taking aspirin and warfarin with a target PT-INR of 2.5 suffered from acute epidural hematoma after falling and underwent successful emergency surgery with intravenous vitamin K infusion. Another 1-year-old-infant taking aspirin and warfarin with a target PT-INR of 2.5 suffered from a huge subcutaneous hematoma and required intravenous vitamin K infusion and fresh frozen plasma because he was found to have developed lupus anticoagulant. Another patient taking aspirin and warfarin suffered from leg bleeding associated with a car accident. The remaining 2 hemorrhagic episodes occurred in a woman taking aspirin, dipyridamole, and warfarin with a target PT-INR of 1.5–2.0 who suffered twice from ovarian bleeding. Minor nose and gum bleeding were often reported, but were not included in the statistical analysis.

Apart from hemorrhagic complications, warfarin treatment was withheld on 9 occasions in 7 patients, because of PT-INR >3.0 without clinical symptoms in 4 and treatment for associated diseases on 5 occasions, including operation for other diseases (2), extraction of teeth (2), and idiopathic thrombocytopenic purpura (1).

Discussion

To date, this is the largest follow-up study of the combination of warfarin and aspirin in patients with GA caused by KD. The results indicate that this therapy has an acceptably high cardiac-event-free survival rate in these patients, though it has a certain risk of hemorrhagic complications.

The cardiac event-free rate was 92.5% at 1 year and 91% at 10 years with the combination treatment regimen, which is comparable to our previous institutional experience in which only 1 of 19 patients on this regimen suffered from AMI, giving 95% AMI-free rate[12] In addition, the fact that 3 patients developed AMI after cessation of warfarin treatment is a real demonstration of the effectiveness of this treatment. In agreement with our result, Onouchi et al[6] reported the efficacy of this regimen in terms of preventing coronary artery occlusion or recanalization in patients with coronary artery aneurysms caused by KD. Though their study had a rather small sample, none of the 11 patients had coronary occlusion or recanalization in a mean follow-up of 9 years. However, there are several issues concerning warfarin treatment in patients with GA caused by KD.

First is the duration of warfarin treatment. It is usually initiated to prevent acute thrombotic occlusion of GA soon after the onset of KD and occlusion of stenotic lesions adjacent to GA late after onset. Within 2 years after onset, patients with KD are known to be in a hypercoagulable state[15,16] In fact, Onouchi et al recorded occlusion or recanalization of coronary artery aneurysms at a mean of 2.5±2.3 years after KD onset without anti-thrombotic treatment and they recommended at least 5 years of the combination regimen[6] On the other hand, in the present study 1 patient suffered from AMI at 7 years after the onset of KD, before he started warfarin treatment, and 1 patient suffered from AMI at 9 years after onset during the time that he had stopped warfarin treatment. Therefore, it might be better to continue patients with GA on warfarin treatment for as long as they have GA or coronary stenosis, unless regression of GA is documented[5] We have to determine the length of warfarin treatment individually in each patient based on the residual coronary pathology.

The second issue is the strength of anticoagulation in balance with the risk of hemorrhagic complications. The guideline of the American Heart Association recommends a target PT-INR of 2.0–2.5[7] but the Japanese Circulation Society recommends 1.2–1.5[8] in patients with GA. In the 6 cardiac events (**Table 3**), the PT-INR before AMI was rather low, ranging from 1.1 to 1.5, and before ICT it ranged from 1.8 to 2.7. On the other hand, as shown in **Table 2**, the lowest PT-INR ranged from 1.0 to 1.6 in all patients and from 1.4 to 1.6 in patients with a target PT-INR of ≥2.0. Therefore, it might be realistic to set the target PT-INR at 2.0 or 2.0–2.5 to prevent AMI, even though this has the substantial risk of coronary thrombus requiring timely ICT.

The third issue is complications, including bleeding. We had a relatively low frequency of hemorrhagic complications at 1.7% patient-year, which is acceptably low compared with anticoagulation for mechanical prosthesis in children, where bleeding complications were 2.9% per patient-year[17] with a target PT-INR of 2.5–3.0. However, we had 2 infants with a target PT-INR of 2.5 who suffered from rather large hemorrhagic complications (epidural hematoma and huge subcutaneous hematoma); however, there were contributing factors other than warfarin. Therefore if we set the target PT-INR at ≥2.5, we may see more

hemorrhagic complications close to the level seen with mechanical prosthesis. Therefore, meticulous care must be taken to avoid accidents, especially in small children who have a higher risk of accidents.

Finally, though we have a retrospective case–control study with a small sample size,[12] there are no prospective randomized controlled trials of combination therapy with warfarin and aspirin in this setting. The best medication for patients with KD complicated by GA must be explored and determined.

Study Limitations

This retrospective descriptive study based on multicenter follow-up did not provide an opportunity to prove the effectiveness of this regimen over other treatment regimens. The protocol of warfarin treatment, including target PT-INR and methods of dose adjustment, was not the same among institutions. However, at least this study provides basic data concerning the mid- to long-term prognosis and complications in KD patients with GA treated by this regimen.

Because all patients received aspirin in combination with warfarin, it was impossible to determine the result of warfarin treatment alone. Also, it was difficult to determine the influence of additional drugs, which were given in only a small number of patients.

Conclusions

Combination therapy of warfarin and aspirin, with a target PT-INR between 1.5 and 2.5, has an acceptably high cardiac-event-free survival rate in patients with GA caused by KD, though it has a certain risk of hemorrhagic complications. It might be better to continue this treatment for as long as the patient has GA, unless there is complete regression.

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References

1. Yanagawa H, Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K. Incidence of Kawasaki disease in Japan: The nationwide surveys of 1999–2002. *Pediatr Int* 2006; **48:** 356–361.
2. Newburger JW, Fulton DR. Kawasaki disease. *Curr Opin Pediatr* 2004; **16:** 508–514.
3. Fukuzawa R, Igeam E, Watanabe M, Hajikano M, Kamisago M, Katsube Y, et al. Coronary artery aneurysm induced by Kawasaki disease in children show features typical senescence. *Circ J* 2007; **71:** 709–715.
4. Nakamura Y, Aso E, Yashiro M, Uehara R, Watanabe M, Oki I, et al. Mortality among persons with a history of Kawasaki disease in Japan: Mortality among males with cardiac sequelae is significantly higher than that of general population. *Circ J* 2008; **72:** 134–138.
5. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease: A 10- to 21-year follow-up study of 594 patients. *Circulation* 1996; **94:** 1379–1385.
6. Onouchi Z, Hamaoka K, Sakata K, Ozawa S, Shiraishi I, Itoi T, et al. Long-term changes in coronary artery aneurysms in patients with Kawasaki disease: Comparison of therapeutic regimens. *Circ J* 2005; **69:** 265–272.
7. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Surgery and Anesthesia; Quality of Care and Outcomes Research Interdisciplinary Working Group. Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116:** 1736–1754.
8. Japanese Circulation Society Joint Research Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease. *Pediatr Int* 2005; **47:** 711–732.
9. van Doorn C, Yates R, Tsang V, de Leval M, Elliott M. Mitral valve replacement in children: Mortality, morbidity, and haemodynamic status up to medium term follow up. *Heart* 2000; **84:** 636–642.
10. Streif ByW, Andrew M, Marzinotto V, Massicotte P, Chan AKC, Julian JA, et al. Analysis of warfarin therapy in pediatric patients: A prospective cohort study of 319 patients. *Blood* 1999; **94:** 3007–3014.
11. Bonduel MM. Oral anticoagulation therapy in children. *Thromb Res* 2006; **118:** 85–94.
12. Sugahara Y, Ishii M, Muta H, Iemura M, Matsuishi T, Kato H. Warfarin therapy for giant aneurysm prevents myocardial infarction in Kawasaki disease. *Pediatr Cardiol* 2008; **29:** 398–401.
13. Levy DM, Silverman ED, Massicotte P, McCrindle BW, Yeung RSM. Long term outcomes in patients with giant aneurysms secondary to Kawasaki disease. *J Rheumatol* 2005; **32:** 928–934.
14. Ikuma H, Wada H, Mori Y. Hemostatic markers in Japanese patients undergoing anticoagulant therapy under thrombotest monitoring. *Blood Coagul Fibrinol* 1999; **19:** 1–6.
15. Sakai M, Asayama K, Otabe T, Kohri T, Shirahata A. Low tissue plasminogen activator relation to plasminogen activator inhibitor-1 as a maker of cardiac complication in children with Kawasaki disease. *Clin Appl Thromb Hemost* 2001; **7:** 214–218.
16. Pucchi A, Martino S, Celeste A, Linari A, Tibaldi M, Camosso E, et al. Angiogenesis, tumor necrosis factor-α and procoagulant factors in coronary artery giant aneurysm of a fatal infantile Kawasaki disease. *Cardiovasc Pathol* 2008; **17:** 186–189.
17. Doorn Cv, Yates R, Tsang V, deLeval M, Elliot M. Mitral valve replacement in children: Mortality, morbidity, and haemodynamic status up to medium term follow up. *Heart* 2000; **84:** 636–642.

Appendix 1

Participating Institutions

Kurume University Hospital; Ehime University Hospital; Kagoshima University Hospital; Kiyose Children's Hospital; Tenri Hospital; Nihon University Hospital; Nihon Medical University Hospital.

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Differentiation Capacity of Endothelial Progenitor Cells Correlates With Endothelial Function in Healthy Young Men

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Background: Endothelial progenitor cells (EPCs) have been assumed to maintain vascular endothelial integrity, so the present study investigated whether the functional capacity of EPCs correlates with endothelial function in healthy young subjects, as has been confirmed in aged subjects with atherosclerotic disease.
Methods and Results: EPCs in 41 healthy, young male nonsmokers (age 33.1±3.9 years, mean±SD) were characterized. The correlation between flow-mediated vasodilation (FMD) and the number of EPCs or the plasma concentrations of growth factors, such as vascular endothelial growth factor, did not reach statistical significance. However, FMD was significantly correlated with the EPC differentiation index, defined as the ratio of the number of EPCs to the total number of adherent cells (r=0.391, P=0.011) and the abundance of endothelial nitric oxide synthase mRNA (r=0.340, P=0.030).
Conclusions: In healthy young men, despite a lack of correlation of the number or colony counts of EPCs, the ability of circulating progenitor cells to differentiate into an endothelial lineage is closely correlated with endothelial function. This cell function assay may serve as a novel biomarker for vascular function in healthy subjects in the pre-atherosclerotic stage. (*Circ J* 2009; **73:** 1324–1329)

Key Words: Angiogenesis; Atherosclerosis; Endothelial function; Endothelial progenitor cells

Circulating progenitor cells (PCs) are potent in differentiating into many different cellular lineages, including all of the cells comprising the vascular wall (ie, endothelial cells, vascular smooth muscle cells, and fibroblasts);[1,2] and are involved in tissue repair and organ viability.[3–6] Recently, endothelial PCs (EPCs) were characterized in detail.[3–7] We have also found that, in patients with primary acute myocardial infarction, the ability of EPCs to differentiate positively correlated with functional improvement and infarct size reduction.[8] Although it is traditionally assumed that replacement of the damaged endothelium results only from outgrowth of preexisting endothelial cells, recent studies have found that PCs mobilized from bone marrow and other putative tissue niches appear to contribute to vascular homeostasis and repair,[9] with the number and colony formation of circulating EPCs inversely correlating with the risk of cardiovascular diseases and positively correlating with endothelial function.[10] The ability of circulating EPCs to form colonies progressively decreases as coronary risk factors increase.[11]

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However, little is known about the degree to which these circulating EPCs are involved in the maintenance of vascular function in healthy young subjects. Furthermore, it is unclear whether the functional characteristics of EPCs correlate with endothelial function in healthy young subjects without obvious atherosclerosis. We consider that circulating EPCs may be more involved in vascular reparative processes than expected, with rapid turnover at endothelial lesions, and that the function of EPCs would directly influence arterial endothelial function. We thus hypothesized that functional EPC characteristics reflect endothelial function, and thereby could serve as an initial biomarker of arteriosclerosis. In the present study, we measured flow-mediated endothelium-dependent vasodilation (FMD) as a marker of endothelial function[12–14] and assessed the association between various EPC characteristics and endothelial function in vivo.

Methods

Study Subjects

We studied 41 healthy young men (age 33.1±3.9 years, range, 25–35), who were all volunteers and free from hypertension, diabetes mellitus, and dyslipidemia. None of them had ever smoked.[15,16] The protocol was reviewed and approved by the Ethics Committee of Nagoya University and the study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent and filled out a questionnaire on their physical

—Review—

Long-Term Prognosis of Patients with Kawasaki Disease: At Risk for Future Atherosclerosis?

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Abstract

Kawasaki disease causes coronary artery lesions, such as dilatation, aneurysms, stenosis, and even occlusion in young children, and is one of the most common acquired heart diseases in developed countries. More than 10,000 new cases are reported in Japan every year. In its acute phase, severe coronary arteritis induces morphological changes in coronary arteries. Treatments for Kawasaki disease aim to eliminate coronary artery inflammation as quickly as possible to reduce the chance of causing coronary lesions. Immunoglobulin therapy with aspirin has become the standard therapy of first choice and helps attenuate coronary lesions. In addition to coronary artery disturbances in the acute phase, sclerotic vascular changes were observed in post-Kawasaki disease patients who did not have coronary lesions in the acute phase. Recent studies have revealed peripheral vasculature endothelial dysfunction in post-Kawasaki disease patients with and without coronary lesions. The risk factors for the development of atherosclerosis in adults, such as C-reactive protein, oxidative stress, and inflammatory cytokines, are also increased in the remote phase of Kawasaki disease. This morphological and functional endothelial dysfunction as Kawasaki disease vascular sequelae may suggest the early development of atherosclerosis in patients with Kawasaki disease. However, no direct evidence for this early development has been found so far. Kawasaki disease was first reported slightly more than 40 years ago. The first documented post-Kawasaki disease patients are now becoming old enough to have atherosclerosis. Some case reports suggest myocardial infarction with atherosclerotic changes in young adults who are believed to have a history of Kawasaki disease. This paper reviews Kawasaki disease from the perspective of long-term prognosis.
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Key words: Kawasaki disease, prognosis, atherosclerosis, cardiac lesion

Introduction

Kawasaki disease (KD) is the most common acquired pediatric cardiac disease in developed countries, and its etiology remains unknown. A national survey of KD has been performed every 2 years since 1970 in Japan. The most recent survey, the 19th, deals with the years 2005 and 2006. The number of new cases of KD in those years was

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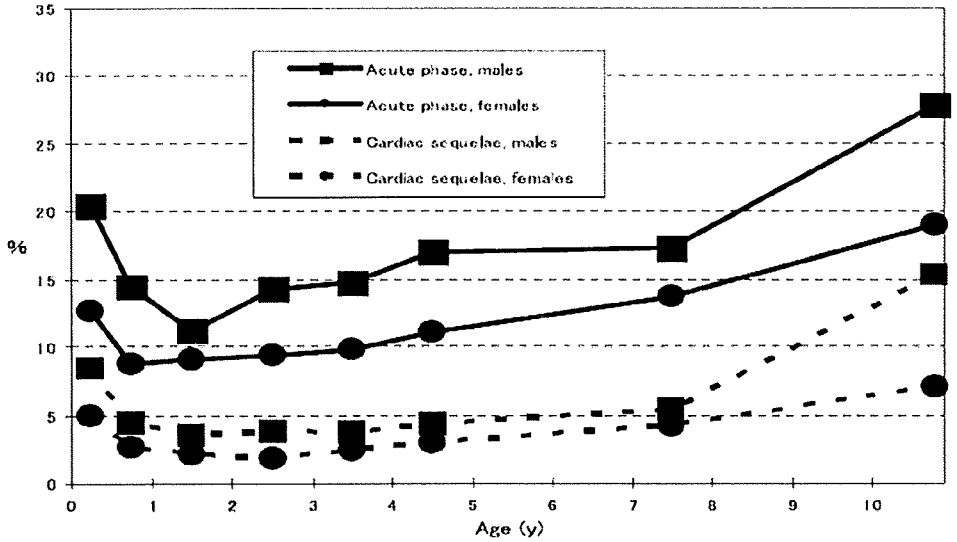

Fig. 1 Age-specific prevalence of cardiac lesions and sequelae due to Kawasaki disease in Japan in 2005–2006 (Nakamura et al., *J Epidemiol* 2008, 18 (4) 167-172)

10,041 and 10,434, respectively[1], for an annual incidence of 184.6 cases per 100,000 people (male, 209.3; female, 158.6). As of 2006, the total number of patients since 1970 was 225,682 (male, 130,827; female, 94,855). Of those patients, more than 90,000 had already reached adulthood.

The incidence of coronary lesions in the acute phase of KD has gradually been decreasing[2]. The incidence was 18.1% from 1997 through 2000 (coronary artery dilatation, 14.7%; aneurysm, 2.9%; and giant aneurysm, 0.50%), 14.8% from 2001 to 2004 (11.6%, 1.5%, and 0.35%), and 11.9% in 2005 and 2006 (10.1%, 1.5%, and 0.35%). KD sequelae, defined as coronary lesions persisting beyond 1 month after KD onset, occurred at a rate of 6.2% from 1997 through 2000 (coronary artery dilatation, 3.9%; aneurysm, 2.9%; and giant aneurysm, 0.50%), 4.5% from 2001 through 2004 (2.8%, 1.3%, 0.35%), and 3.7% in 2005 and 2006 (2.3%, 1.0%, 0.35%). These improvements can mainly be attributed to advances in intravenous immunoglobulin therapy (IVIG). In Japan, 86% of patients with KD are treated with IVIG, and a single IVIG dose of 2.0 g/kg is selected in 68% of cases. The proportions of the cardiac lesions were higher in males than in females, and among infants and old patients (**Fig. 1**). Although the incidence of coronary sequelae has gradually been decreasing, the rate of severe sequelae, such as giant aneurysms, has not been decreasing as expected. Determining how to reduce severe sequelae should be the next step in dealing with KD.

Cardiac Sequelae of Kawasaki Disease: A Natural History

Formation of Coronary Aneurysms

High echodensity of the coronary artery wall was observed in all patients with KD at a mean of 5.4 days from disease onset[3]. In the past, when IVIG was not the standard therapy and patients were treated only with aspirin, diffuse coronary artery dilatation occurred in 50% of patients with KD at a mean of 9.5 days from onset. Furthermore, diffuse coronary artery dilatation progresses to aneurysms in 28.8% of patients at a mean of 11.4 days from onset. When coronary artery dilatation resolves within 30 days from onset, the dilatation is called "transient dilation". Coronary lesions that persist beyond 30 days from onset are considered KD sequelae. **Table 1** shows the coronary aneurysm classification in Japan.

Inflammatory cells invade the intima and destroy the internal elastic lamina and continue to infiltrate the tunica media. With inflammatory cell invasion from the adventitia, panvasculitis develops. The internal elastica and external elastica become

Table 1

(a) Classification of coronary aneurysms

1) Small Aneurysm (ANs) or Dilatation (Dil): inside diameter of regional coronary artery is less than 4 mm, or less than 1.5 times wider compared to adjacent vasculature in patients over 5 years of age.
2) Medium-sized Aneurysm (ANm): inside diameter is greater than 4 mm but less than or equal to 8 mm, or is 1.5 to 4.0 times wider compared to adjacent vasculature in patients over 5 years of age.
3) Giant Aneurysm (ANl): inside diameter is greater than 8 mm, or is more than 4 times wider in patients over 5 years of age.

(b) Classification of Severity

Coronary artery lesion severity was classified into five classes below, according to echocardiogram or coronary artery angiogram results.

1) No dilated coronary artery lesion.
2) Transient coronary artery dilatation in acute phase: a case of coronary artery dilatation is restored to normal within 30 disease days.
3) Regression: small to giant aneurysm persists beyond 30 disease days and returns to normal within one year from onset of the disease. (Coronary artery stenosis group cases excluded.)
4) Residual aneurysm: aneurysm persisted beyond one year from onset. (Coronary artery stenosis group cases excluded.)
5) Coronary artery stenosis: a case of coronary artery stenosis was observed by coronary artery angiogram.
   5-1) Coronary artery stenosis without myocardial ischemia
   5-2) Coronary artery stenosis with myocardial ischemia

Reference materials: specific comments are added to coronary artery lesion severity classes when a case has more than moderate valvular disease, heart failure, or severe arrhythmia.

fragmented, and when aortic blood pressure becomes unbearably high, aneurysm formation begins[4]. Histopathological investigations have shown 5 stages in the morphogenesis of arteritis: 1) endothelial degeneration and increased vascular permeability; 2) edema and degeneration of the media; 3) necrotizing panarteritis; 4) granulation formation; and 5) scar formation[5]. Aneurysm formation is likely to occur at the coronary artery branches, where atherosclerotic lesions are also likely to occur[6]. Reducing shear stress in aneurysms and in coronary artery branches is considered to be a mechanism facilitating aneurysm formation[7]. Furthermore, metalloproteinase (MMP)-9 expression not accompanied by an increase in the tissue inhibitor of metalloproteinase (TIMP)-1 contributes greatly to the development of aneurysms[8].

IVIG therapy contributes significantly to the reduction of cardiac sequelae and has becomes the universal standard treatment for KD[9-12]. The mechanism for the effectiveness of IVIG remains unknown; however, even in cases with positive responses to IVIG, aneurysms still occasionally form. Echocardiography should be performed at around the 30th disease day to check for KD sequelae.

Fate of Coronary Aneurysms

Regression

Most aneurysms tend to decrease in size. When an aneurysm disappears and the coronary artery looks normal, this is called "regression"[13]. Small- to medium-sized aneurysms are likely to regress within 1 to 2 years after disease onset. The frequency of this regression is 32% to 50%[14,15]. Regression is mainly the result of smooth muscular cell infiltration and proliferation in the intima[16]. Sequential coronary angiography performed 10 to 20 years after regression shows no significant stenosis[13,17]. Cases showing regression are supposed to be considered cured, and follow-up may be discontinued. However, recent reports confirm regional stenosis has occurred at regions of regression in 3 of 210 cases 8 to 10 years after disease onset[18]. In addition to morphological changes such as intimal thickening[4,18,19], reduced dilatation ability[18] and abnormal endothelial cell function[20,21] have been reported at regions of regression. Furthermore, the possibility of

atherosclerosis developing has also been suggested[22].

Occlusion

Occlusion is often observed in medium-sized or larger coronary aneurysms. Suzuki et al. have reported that 16% of coronary aneurysms are occluded at follow-up, 78% of which became occluded within 2 years from onset[23]. Whereas acute myocardial infarctions and sudden deaths have been caused by coronary artery occlusion, two-thirds of patients with occlusion have no symptomatic episodes[23]. This is a characteristic finding of KD which is consistent with histological findings, such as recanalization and well-developed collateral arteries[24].

Revascularization

Neovascularization after occlusion is called segmental stenosis. Segmental stenosis has been observed in 15% of patients with KD sequelae, 90% of which occurred in the right coronary artery[23]. The right coronary artery is occluded or revascularized more easily than the left coronary artery. Vessels revascularized after total thrombotic occlusion express vascular growth factors, which suggests that active remodeling continues in the remote phase of KD[25].

Regional Stenosis

Suzuki et al. have reported that severe regional stenosis was present at coronary angiography in 12% of 200 patients[26]. They found that regional stenosis was especially significant in the territory of the left anterior descending artery (LAD). Another group has reported regional stenosis in 4.7% of 594 patients with KD after 10 to 21 years[27]. Regional stenosis usually occurs in both the inflow and outflow shoulders of the aneurysm. Regional stenosis is caused mainly by inward luminal intimal thickening. Vascular growth factor expression is observed in vascular smooth muscle cells and microvasculature at stenosis site, which suggests active vascular remodeling is still ongoing even in the remote phase of KD[25]. Large aneurysms tend to lead to stenosis. However, even small aneurysms, such as one of 5.6 mm, lead to stenosis after a long follow-up period[15]. Intravascular Ultrasound Scope (IVUS) showed the possibility of developing stenosis in the coronary artery with intimal thickening over 4 mm[28].

Coronary Arteries without Aneurysms

Coronary arteries that appear normal from the onset of KD have been regarded as normal, so far. However, some reports have stated mild-to-moderate intimal thickening has been observed in coronary arteries without aneurysms[16,18]. A considerable amount of controversy remains surrounding the issue of whether a history of KD itself is a risk factor for future atherosclerosis.

The Long-Term Prognosis of KD

Only 40 years have passed since KD was first reported by Kawasaki[29]. Because KD mainly afflicts infants or young children, there are too few post-KD patients for proper cardiovascular investigations. One of the most conceivable issues for the long-term prognosis of KD is that the disease may represent a risk factor for atherosclerosis. KD is characterized by severe systemic vasculitis, and the post-inflammatory vasculature may not return to completely normal tissues. Because atherosclerosis is proven to be an inflammatory disorder[30], many similarities have been found in the status post-KD patients. Negro et al[31]. have reported 2 cases of acute coronary disease in young adults who had KD more than 20 years earlier. Coronary artery sequelae of KD, such as aneurysms, were not detected. Both cases were believed to be caused by atherosclerosis. However, there is no direct evidence demonstrating that KD represents a risk factor for atherosclerosis.

We have stated that typical intimal thickening in KD aneurysms is a result of active vascular remodeling. Intimal thickening is also observed in patients with KD who have normal-appearing coronary arteries[4,16]. Severe coronary arteritis denuded coronary endothelial cells at the site of aneurysm[31], but the endothelial cells themselves recovered within a few years[33]. However, recovered endothelial cells were deficient in physiological functional proteins, such as endothelial nitric oxide synthase (eNOS)[33]. The function of recovered

endothelial cells is questionable. In addition to intimal thickening in coronary lesions in patients with KD, vascular findings similar to atherosclerosis, such as vascular senescence[33] and expression of adhesion molecules[32,33] and growth factors[25,34], suggest that KD is a risk factor for atherosclerosis. In this article, we reviewed the long-term prognosis of KD vasculature from the viewpoint of its possible relationship with atherosclerosis.

The Importance of Endothelial Dysfunction for Atherosclerosis Development

Ross outlined a response-to-injury hypothesis for the development of atherosclerosis[30]. In this theory, he suggested endothelial injury and endothelial dysfunction were the keys to atherosclerosis development. Inflammatory reaction is generated by endothelial injury and induces endothelial dysfunction. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified low-density lipoprotein (LDL) cholesterol; free radicals caused by cigarette smoking, hypertension, diabetes mellitus and genetic alterations; elevated plasma homocystine concentrations; and infectious microorganisms, such as herpes viruses or *Chlamydia pneumoniae*; or combinations of these or other factors[30]. Endothelial dysfunction that results from injury leads to compensatory responses that alter the normal homeostatic properties of the endothelium. Thus, the different forms of injury increase the adhesiveness of the endothelium to leukocytes or platelets and increase its permeability. The injury also induces the endothelium to have procoagulant instead of anticoagulant properties and to form vasoactive molecules, cytokines, and growth factors[30]. Therefore, endothelial injury and dysfunction initiate the reactions for atherosclerosis progression, such as the migration and proliferation of smooth muscle cells, intimal thickening, macrophage invasion, foam cell transformation, deposition of oxidized LDL, and, finally, atherosclerotic plaque formation.

Previous studies of KD focused mainly on the morphological changes of coronary arteries. Recently, vascular functional studies of KD have been undertaken and there is now evidence of endothelial dysfunction even many years after the onset of KD. The post-KD vasculature has many similarities with atherosclerosis. We are introducing what is being discussed surrounding the issue of KD vasculature a long time after disease onset.

Vascular Elasticity

It is well known that vascular stiffness is increased in atherosclerotic vasculature. Vascular elasticity is degraded by endothelial dysfunction, intimal thickening, and by an increase in the vascular wall extracellular matrix. The loss of vascular elasticity is estimated to be a poor response to a vascular dilator. The coronary artery response to acetylcholine or isosorbide has been well documented as a marker for endothelial dysfunction. Isosorbide induces dilatation of both arteries and veins in an endothelium-independent manner. In patients with KD who have normal coronary arteries, coronary artery dilatation induced by isosorbide is no different from that in healthy persons. However, poorer coronary artery dilatation was noted according to the severity of coronary artery sequelae[17,35]. On the other hand, acetylcholine dilates arteries in an endothelium-dependent manner. When the endothelium is injured, the coronary artery shows constriction by acetylcholine, which indicates endothelium dysfunction. The reaction to acetylcholine of normal-appearing coronary arteries in patients with KD is equivalent to that of the control. However, the response to acetylcholine infusion of a coronary artery with a KD aneurysm or stenosis or both is poor dilatation or even constriction[17,20,21].

Noninvasive evaluations of vascular elasticity have also been well documented. Pulse wave velocity (PWV) and percentage change of flow-mediated dilatation (%FMD) are representative studies for evaluating arterial stiffness. The PWV is simple to measure and is a good biomarker for the risk of atherosclerosis in adults[36]. The PWV indicates the transit time required for a pulse to travel from the brachial artery at the elbow to the radial artery at the wrist. The PWV is related to the square root of the elastic modulus, according to the Moens-Korteweg equation[37]. The stiffer the artery becomes,

the faster the PWV will be. There are several reports that show PWV is especially high in patients with KD who have coronary aneurysms[38-41]. However, PWV does not differ significantly between patients with normal-appearing coronary arteries and healthy persons.

The %FMD reflects endothelial NO-dependent vasodilatation. The simulation for %FMD is provided by reactive hyperemia in the brachial artery with a cuff on the forearm inflated to greater than the systolic blood pressure for 5 minutes. A longitudinal section of the brachial artery is scanned 2 to 5 cm above the elbow with 2-dimensional ultrasonography. The diameter of the brachial artery at rest and immediately after 5 minutes of blood flow occlusion is evaluated, and the percent change of the diameter is calculated. Decreased %FMD reflects endothelial cell dysfunction, and a significant decrease in %FMD is a common feature in adult atherosclerosis[42]. Decreased %FMD in patients with KD has also been reported by multiple facilities[40,43,44]. Decreased %FMD was not found to correlate with the features of acute KD illness[44] but is related to the severity of coronary aneurysm[40,43].

Increased Carotid Intima-Media Thickness

Intima-media thickness (IMT) has been shown to reliably indicate the presence of atherosclerosis. IMT is determined with 2-dimensional ultrasonography of the carotid artery. The thicker the IMT, the higher the risk of atherosclerosis becomes. The IMT is also greater in patients with KD[39,45,46], and the IMT correlates with the severity of aneurysms in KD.

Above those reports we reviewed so far, claimed that these poor vascular elasticity findings in KD patients suggested a persistence of endothelial dysfunction, and the possibility for a future early onset of atherosclerosis. However, the studies suggesting negative findings of IMT or %FMD or both in patients with KD have also been reported[17,47].

Dyslipidemia

One of the strongest risk factors for atherosclerosis is dyslipidemia. Higher levels of LDL cholesterol, triglyceride, and total cholesterol, along with a lower level of high-density lipoprotein (HDL) cholesterol are strong cardiovascular risk factors for atherosclerosis. Dyslipidemia has also been reported in patients with KD[38,39]. However, others[40,46,47] did not confirm dyslipidemia in patients with KD with or without overt coronary artery sequelae well beyond the time that the clinical disease had been resolved. Intriguingly, invaded macrophage in intima, which is the key player in atherosclerotic plaque formation, was not detected in coronary arteries in KD patients 3 to 12 years after onset[25,33]. Therefore, it is not certain that the dyslipidemia in KD patients causes a higher risk of atherosclerosis than in other people. However, there were not enough data of KD patients afflicted over a decade ago. Epidemiologic studies among elderly people are necessary for discussing the risk of KD for dyslipidemia and atherosclerosis.

Persisting Vascular Inflammation and Increased Oxidative Stress

Atherosclerosis is fundamentally an inflammatory disorder[30]. Inflammatory biomarkers, such as C-reactive protein (CRP)[48,49], myeloperoxidase (MPO)[50,51], or Pentraxin (PTX)-3[52] are elevated and are counted as risk factors for atherosclerosis. In addition, CRP[53] and MPO[51] themselves promote atherosclerosis. Patients with persistent coronary artery aneurysms have been shown to have ongoing systemic inflammation years after disease onset, as evidenced by significantly elevated CRP levels in a large cohort[54]. However, a study treating CRP levels in a relatively small cohort of KD patients could not show a significant difference[40].

Several lines of evidence suggest that oxidative stress may promote endothelial dysfunction through increased production of reactive oxygen species (ROS)[55]. *In vitro* studies unequivocally demonstrate that all vascular cells produce ROS and that ROS mediate diverse physiological functions in cells[56]. Furthermore, ROS play a role in the development of vasculopathies, including atherosclerosis. There are several ways to monitor total ROS generation *in vivo*. In earlier studies, these have included the measurement of thiobarbituric acid-reacting substances in blood samples, including malonyldialdehyde (MDA), and chemically stable

substances in urine, such as F_2 isoprostanes $iPF_{2\alpha}$-III (formerly known as 8-*iso*-prostaglandin $F_{2\alpha}$). Because MDA is a byproduct of cyclooxygenase (COX) turnover and $iPF_{2\alpha}$-III is somewhat formed by COX-1 and -2, they are not strictly reflected in regional ROS generation. However, they are regarded as good *in vivo* biomarkers as a quantification of basal ROS generation in many diseases. An increased level of $iPF_{2\alpha}$-III is associated with atherosclerosis risk factors, such as hypercholesterolemia[57], cigarette smoking[58], diabetes mellitus[59], renovascular hypertension[60], and hyperhomocysteinemia[61]. Urinary $iPF_{2\alpha}$-III is increased long after the onset of KD[62], as well as after acute phase KD[63]. Cheung et al. revealed significantly higher serum levels of MDA and hydroperoxides in children long after KD onset[64].

Histological Examinations

Histological examinations of atherosclerotic plaque have been well documented. Besides morphologic changes, such as intimal thickening and atherosclerotic plaque formation, characteristic features of atherosclerosis are classified as follows: a decrease in physiological functional substances such as eNOS; macrophage invasion and foamy cell transformation; LDL oxidation; and increased expression of growth factors, adhesion molecules, chemokines and cytokines. Among these histological findings, similarities and differences in KD coronary arteries have been determined. Inflammatory cell invasions, which suggest persisting coronary artery vasculitis, were not detected in coronary arteries many years after the onset of KD[25,32,33]. Takahashi et al. reported typical atherosclerotic plaque in a young adult, strongly suspecting a history of KD 19 years earlier[16]. Atherosclerotic plaque was determined in culprit lesion of acute coronary syndrome in KD patients afflicted 30 years previously[31]. However, significant macrophage infiltration or foamy cell formation was not observed in KD coronary arteries around ten years after the onset of KD[25,33,34]. Even the fatty streak, one of the earliest findings in atherosclerosis, was not detected in KD coronary arteries[25]. The few macrophages and the lack of lipid deposition were major differences between adult atherosclerosis and coronary arteries less than 10 years after the onset of KD. Therefore, a study of coronary arteries more than a decade after being afflicted with KD is greatly needed.

Other features of atherosclerosis were detected in KD coronary arteries with minor differences. The coronary artery endothelium was denuded in the acute phase of KD aneurysm[32] and recovered without the expression of functional proteins such as eNOS[33]. Growth factor expressions, transforming growth factor (TGF) β1, platelet-derived growth factor (PDGF)-A, basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), were observed on smooth muscle cells in intima at coronary lesions[25,34]. The adhesion molecule vascular cell adhesion molecule (VCAM)-1 was mainly expressed only in neovasculature in acute phase KD[32], and was also identified on the recovered endothelium of KD aneurysms[33]. Growth factors and adhesion molecules were mainly expressed in the vaso vasorum and in neoangiogenesis in KD patients. On the other hand, these growth factor and adhesion molecule expressions were mainly admitted around intimal plaque in cases of atherosclerosis. Fukazawa et al. reported that vascular senescence increased in KD aneurysms[33]. The findings of vascular senescence, detected in the increased β-galactosidase activity and closely associated with atherosclerosis[65,66], include increased adhesion molecules and pro-inflammatory cytokines or chemokines, as well as a reduction of normal physiological vascular proteins, such as eNOS or prostacyclins. Their senescence findings in KD patients were severe in the vasculature of vasa vasorum as well as in intimal endothelial cells, which were thought to be unique to KD and different from that of adult atherosclerosis lesions. While adult atherosclerosis progression originates on the intimal side of the arteries, the atherosclerotic change of the KD aneurysm may develop from the adventitial vasa vasorum[33].

Experimental Coronary Arteritis Facilitates the Development of Atherosclerosis

Animal models of coronary arteritis showed a history of arteritis can be a risk factor for

atherosclerosis development. Allergic coronary arteritis in rabbits induced by serial horse serum injections showed typical panarteritis: inflammatory cell invasion of both sides from intima and adventitia, medial edema, and destruction of internal elastic lamina[67]. Intimal thickness with the small muscle cell (SMC) persisted even in the chronic phase, when inflammatory cells have subsided. When a high fat diet was being fed to this allergic arteritis rabbit model, typical atherosclerotic plaque appeared significantly[67]. This finding suggested post-arteritis tissue may more easily develop atherosclerotic changes.

Summary

We reviewed the problems of coronary lesions in acute phase KD as well as the possibility of early atherosclerosis long after KD onset. The risk factors for atherosclerosis have already appeared in the vasculature of patients with a history of KD. The major difference so far is the lack of lipid deposits and typical atherosclerotic plaque in KD vasculature. However, it is still too early to obtain dependable data, because most of the patients studied thus far were less than 10 years from the onset of KD. Only some case reports have suggested definite pathological findings of atherosclerosis in young adult patients with KD histories. Nonetheless, patients with a history of KD should be more careful to reduce the risks of atherosclerosis by staying healthy, dieting, exercising, and refraining from smoking. It has been over 40 years since KD was discovered and the earliest patients have only just reached the potential age for atherosclerosis. Reliable epidemiologic data are expected to appear soon.

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References

1. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H: Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005-2006. J Epidemiol 2008; 18: 167–172.
2. Yashiro M, Uchara R, Oki I, et al.: Yearly Changes in Gamma Globulin Treatment for Kawasaki Disease Patients, 1993-2002. Nippon Shonika Gakkai Zasshi 2004; 108: 1461–1466.
3. Kamiya T, Suzuki A, Kijima Y, Hirose O, Takahashi O: Coronary Arterial Lesion in Kawasaki Disease—Occurence and Prognosis—. Junkankibyo Kenkyu no Shinpo 1982; 3: 19–27.
4. Naoe S, Takahashi K, Masuda H, Tanaka N: Kawasaki disease. With particular emphasis on arterial lesions. Acta Pathol Jpn 1991; 41: 785–797.
5. Amano S, Hazama F, Hamashima Y: Pathology of Kawasaki disease: I. Pathology and morphogenesis of the vascular changes. Jpn Circ J 1979; 43: 633–643.
6. Tanaka N, Naoe S, Masuda H, Ueno T: Pathological study of sequelae of Kawasaki disease (MCLS). With special reference to the heart and coronary arterial lesions. Acta Pathol Jpn 1986; 36: 1513–1527.
7. Ohkubo T, Fukazawa R, Ikegami E, Ogawa S: Reduced shear stress and disturbed flow may lead to coronary aneurysm and thrombus formations. Pediatr Int 2007; 49: 1–7.
8. Gavin PJ, Crawford SE, Shulman ST, Garcia FL, Rowley AH: Systemic arterial expression of matrix metalloproteinases 2 and 9 in acute Kawasaki disease. Arterioscler Thromb Vasc Biol 2003; 23: 576–581.
9. Furusho K, Kamiya T, Nakano H, et al.: High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984; 2: 1055–1058.
10. Furusho K, Sato K, Soeda T, et al.: High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1983; 2: 1359.
11. Newburger JW, Takahashi M, Beiser AS, et al.: A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991; 324: 1633–1639.
12. Newburger JW, Takahashi M, Burns JC, et al.: The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986; 315: 341–347.
13. Kato H, Koike S, Yamamoto M, Ito Y, Yano E: Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. J Pediatr 1975; 86: 892–898.
14. Sasaguri Y, Kato H: Regression of aneurysms in Kawasaki disease: a pathological study. J Pediatr 1982; 100: 225–231.
15. Suzuki A, Kamiya T, Arakaki Y, Kinoshita Y, Kimura K: Fate of coronary arterial aneurysms in Kawasaki disease. Am J Cardiol 1994; 74: 822–824.
16. Takahashi K, Oharaseki T, Naoe S: Pathological study of postcoronary arteritis in adolescents and young adults: with reference to the relationship between sequelae of Kawasaki disease and

atherosclerosis. Pediatr Cardiol 2001; 22: 138–142.
17. Iemura M, Ishii M, Sugimura T, Akagi T, Kato H: Long term consequences of regressed coronary aneurysms after Kawasaki disease: vascular wall morphology and function. Heart 2000; 83: 307–311.
18. Suzuki A, Yamagishi M, Kimura K, et al.: Functional behavior and morphology of the coronary artery wall in patients with Kawasaki disease assessed by intravascular ultrasound. J Am Coll Cardiol 1996; 27: 291–296.
19. Sugimura T, Yokoi H, Sato N, et al.: Interventional treatment for children with severe coronary artery stenosis with calcification after long-term Kawasaki disease. Circulation 1997; 96: 3928–3933.
20. Mitani Y, Okuda Y, Shimpo H, et al.: Impaired endothelial function in epicardial coronary arteries after Kawasaki disease. Circulation 1997; 96: 454–461.
21. Yamakawa R, Ishii M, Sugimura T, et al.: Coronary endothelial dysfunction after Kawasaki disease: evaluation by intracoronary injection of acetylcholine. J Am Coll Cardiol 1998; 31: 1074–1080.
22. Naoe S, Masuda H: Kawasaki Disease as a Risk Factor for Early Onset Athelosclerosis—From Pathological Stand Point of View—. Doumyakukoka 1981; 9: 27–31.
23. Suzuki A, Kamiya T, Tsuda E, Shinya T: Natural history of coronary arterial lesions in Kawasaki disease. Prog Pediatr Cardiol 1997; 6: 211–218.
24. Suzuki A, Kamiya T, Ono Y, Kinoshita Y, Kawamura S, Kimura K: Clinical significance of morphologic classification of coronary arterial segmental stenosis due to Kawasaki disease. Am J Cardiol 1993; 71: 1169–1173.
25. Suzuki A, Miyagawa-Tomita S, Komatsu K, et al.: Active remodeling of the coronary arterial lesions in the late phase of Kawasaki disease: immunohistochemical study. Circulation 2000; 101: 2935–2941.
26. Suzuki A, Kamiya T, Ono Y, Kohata T, Kimura K, Takamiya M: Follow-up study of coronary artery lesions due to Kawasaki disease by serial selective coronary arteriography in 200 patients. Heart Vessels 1987; 3: 159–165.
27. Kato H, Sugimura T, Akagi T, et al.: Long-term Consequences of Kawasaki Disease: A 10- to 21-Year Follow-up Study of 594 Patients. Circulation 1996; 94: 1379–1385.
28. Tsuda E, Kamiya T, Kimura K, Ono Y, Echigo S: Coronary artery dilatation exceeding 4.0 mm during acute Kawasaki disease predicts a high probability of subsequent late intima-medial thickening. Pediatr Cardiol 2002; 23: 9–14.
29. Kawasaki T: Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of fingers and toes in children. Arerugi 1967; 16: 178–222, 225.
30. Ross R: Atherosclerosis—an inflammatory disease. N Engl J Med 1999; 340: 115–126.
31. Negoro N, Nariyama J, Nakagawa A, et al.: Successful Catheter Interventional Therapy for Acute Coronary Syndrome Secondary to Kawasaki Disease in Young Adults. Circ J 2003; 67: 362–365.
32. Miura M, Garcia FL, Crawford SE, Rowley AH: Cell adhesion molecule expression in coronary artery aneurysms in acute Kawasaki disease. Pediatr Infect Dis J 2004; 23: 931–936.
33. Fukazawa R, Ikegam E, Watanabe M, et al.: Coronary artery aneurysm induced by Kawasaki disease in children show features typical senescence. Circ J 2007; 71: 709–715.
34. Suzuki A, Miyagawa-Tomita S, Komatsu K, et al.: Immunohistochemical study of apparently intact coronary artery in a child after Kawasaki disease. Pediatrics International 2004; 46: 590–596.
35. Sugimura T, Kato H, Inoue O, Takagi J, Fukuda T, Sato N: Vasodilatory response of the coronary arteries after Kawasaki disease: evaluation by intracoronary injection of isosorbide dinitrate. J Pediatr 1992; 121 (5 Pt 1): 684–688.
36. Wang X, Keith JC Jr, Struthers AD, Feuerstein GZ: Assessment of arterial stiffness, a translational medicine biomarker system for evaluation of vascular risk. Cardiovasc Ther 2008; 26: 214–223.
37. Nicholes WW, O'Rourke MF: Vascular Impedence. In McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles, 4th Edition. 1998; pp 54–57, 243–293, Edward Arnold, London.
38. Cheung YF, Yung TC, Tam SC, Ho MH, Chau AK: Novel and traditional cardiovascular risk factors in children after Kawasaki disease: implications for premature atherosclerosis. J Am Coll Cardiol 2004; 43: 120–124.
39. Cheung YF, Wong SJ, Ho MHK: Relationship between carotid intima-media thickness and arterial stiffness in children after Kawasaki disease. Arch Dis Child 2007; 92: 43–47.
40. Niboshi A, Hamaoka K, Sakata K, Yamaguchi N: Endothelial dysfunction in adult patients with a history of Kawasaki disease. Eur J Pediatr 2008; 167: 189–196.
41. Ooyanagi R, Fuse S, Tomita H, et al.: Pulse wave velocity and ankle brachial index in patients with Kawasaki disease. Pediatr Int 2004; 46: 398–402.
42. Al-Qaisi M, Kharbanda RK, Mittal TK, Donald AE: Measurement of endothelial function and its clinical utility for cardiovascular risk. Vasc Health Risk Manag 2008; 4: 647–652.
43. Ikemoto Y, Ogino H, Teraguchi M, Kobayashi Y: Evaluation of preclinical atherosclerosis by flow-mediated dilatation of the brachial artery and carotid artery analysis in patients with a history of Kawasaki disease. Pediatr Cardiol 2005; 26: 782–786.
44. Dhillon R, Clarkson P, Donald AE, et al.: Endothelial Dysfunction Late After Kawasaki Disease. Circulation 1996; 94: 2103–2106.
45. Noto N, Okada T, Yamasuge M, et al.: Noninvasive assessment of the early progression of atherosclerosis in adolescents with Kawasaki disease and coronary artery lesions. Pediatrics 2001; 107: 1095–1099.
46. Dalla Pozza R, Bechtold S, Urschel S, Kozlik-Feldmann R, Netz H: Subclinical atherosclerosis, but normal autonomic function after Kawasaki disease. J Pediatr 2007; 151: 239–243.
47. McCrindle BW, McIntyre S, Kim C, Lin T, Adeli K: Are patients after Kawasaki disease at increased risk for accelerated atherosclerosis? J Pediatr 2007; 151: 244–248, 248 e241.
48. Libby P, Ridker PM, Maseri A: Inflammation and atherosclerosis. Circulation 2002; 105: 1135–1143.

49. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003; 107: 391–397.
50. Baldus S, Heeschen C, Meinertz T, et al.: on behalf of the CAPTURE Investigators: Myeloperoxidase Serum Levels Predict Risk in Patients With Acute Coronary Syndromes. Circulation 2003; 108: 1440–1445.
51. Meuwese MC, Stroes ES, Hazen SL, et al.: Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study. J Am Coll Cardiol 2007; 50: 159–165.
52. Savchenko A, Imamura M, Ohashi R, et al.: Expression of pentraxin 3 (PTX3) in human atherosclerotic lesions. J Pathol 2008; 215: 48–55.
53. Libby P, Ridker PM: Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med 2004; 116(Suppl 6A): 9S–16S.
54. Mitani Y, Sawada H, Hayakawa H, et al.: Elevated Levels of High-Sensitivity C-Reactive Protein and Serum Amyloid-A Late After Kawasaki Disease: Association Between Inflammation and Late Coronary Sequelae in Kawasaki Disease. Circulation 2005; 111: 38–43.
55. Griendling KK, FitzGerald GA: Oxidative Stress and Cardiovascular Injury: Part II: Animal and Human Studies. Circulation 2003; 108: 2034–2040.
56. Griendling KK, FitzGerald GA: Oxidative Stress and Cardiovascular Injury: Part I: Basic Mechanisms and In Vivo Monitoring of ROS. Circulation 2003; 108: 1912–1916.
57. Reilly MP, Pratico D, Delanty N, et al.: Increased Formation of Distinct F2 Isoprostanes in Hypercholesterolemia. Circulation 1998; 98: 2822–2828.
58. Morrow JD, Frei B, Longmire AW, et al.: Increase in Circulating Products of Lipid Peroxidation (F2-Isoprostanes) in Smokers—Smoking as a Cause of Oxidative Damage. N Engl J Med 1995; 332: 1198–1203.
59. Davi G, Ciabattoni G, Consoli A, et al.: In Vivo Formation of 8-Iso-Prostaglandin F2{alpha} and Platelet Activation in Diabetes Mellitus: Effects of Improved Metabolic Control and Vitamin E Supplementation. Circulation 1999; 99: 224–229.
60. Minuz P, Patrignani P, Gaino S, et al.: Increased Oxidative Stress and Platelet Activation in Patients With Hypertension and Renovascular Disease. Circulation 2002; 106: 2800–2805.
61. Davi G, Di Minno G, Coppola A, et al.: Oxidative Stress and Platelet Activation in Homozygous Homocystinuria. Circulation 2001; 104: 1124–1128.
62. Niboshi A, Sakata K, Hamaoka K: Vascular Endothelial Dysfunction and Oxidative Stress Late after Onset of Kawasaki Disease. Circulation Journal 2006; 70(Suppl.I): 471.
63. Takeuchi D, Saji T, Takatsuki S, Fujiwara M: Abnormal tissue doppler images are associated with elevated plasma brain natriuretic peptide and increased oxidative stress in acute Kawasaki disease. Circ J 2007; 71: 357–362.
64. Cheung YF, O K, Woo CW, et al.: Oxidative stress in children late after Kawasaki disease: relationship with carotid atherosclerosis and stiffness. BMC Pediatr 2008; 8: 20.
65. Minamino T, Miyauchi H, Yoshida T, Ishida Y, Yoshida H, Komuro I: Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction. Circulation 2002; 105: 1541–1544.
66. Minamino T, Miyauchi H, Yoshida T, Tateno K, Komuro I: The role of vascular cell senescence in atherosclerosis: antisenescence as a novel therapeutic strategy for vascular aging. Curr Vasc Pharmacol 2004; 2: 141–148.
67. Liu Y, Onouchi Z, Sakata K, Ikuta K: An Experimental Study on the Role of Smooth Muscle Cells in the Pathogenesis of Atherosclerosis of the Coronary Arteritis. Nippon Shonika Gakkai Zasshi 1996; 100: 1453–1458.

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—Case Reports—

Two Cases of Restrictive Cardiomyopathy in Children

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Abstract

A 3-year-old girl was diagnosed with restrictive cardiomyopathy (RCM) after showing symptoms of heart failure, and a 6-year-old boy was found to have RCM after abnormal electrocardiographic findings were seen during school-based heart disease screening. Both had typical clinical features of the disease. Plasma levels of brain natriuretic peptide increased significantly in both patients, allowing us to distinguish this disease from constrictive pericarditis which has similar clinical and hemodynamic features. The early diastolic mitral annular velocity recorded by tissue Doppler echocardiography was also useful to discriminate RCM from constrictive pericarditis. The former case successfully received heart transplantation, but the latter case died suddenly prior to receiving a heart transplant. The plasma level of brain natriuretic peptide and tissue Doppler echocardiography helped us to diagnose this disease earlier and follow it more carefully, which has important implications in optimal treatment and improved prognosis of RCM in children.
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Key words: restrictive cardiomyopathy, brain natriuretic peptide, tissue Doppler echocardiography

Introduction

Restrictive cardiomyopathy (RCM) is a primary heart-muscle disease characterized by impaired ventricular filling with normal or decreased diastolic ventricular volume. Left ventricular systolic function usually remains normal, at least in the early phase of the disease, and the thickness of the left ventricle wall is within the normal range. It is a rare form of cardiomyopathy in childhood, accounting for between 2–5% of idiopathic cardiomyopathy in that age group[1,2]. It is often difficult to distinguish RCM from constrictive pericarditis, because of similar clinical features and similar ventricular diastolic filling hemodynamics. RCM may progress rapidly in childhood[3,4] and heart transplantation is the only reliable treatment in such cases. We report two cases of RCM, both with rapid progression to heart failure. The plasma level of brain natriuretic peptide (BNP) and the early diastolic mitral annular velocity (e') recorded by tissue Doppler echocardiography were found to be useful for diagnosis and follow-up of RCM.

Case 1

A 3-year-old girl was referred to our hospital with

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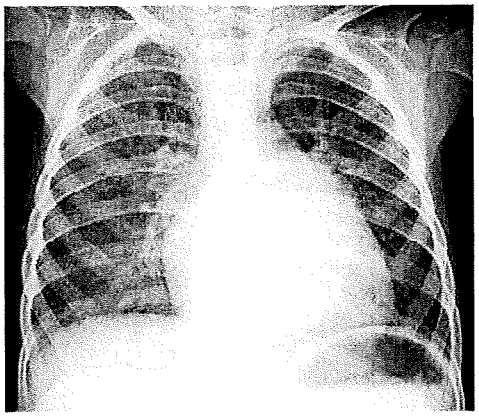

Fig. 1A Chest radiograph shows a cardiothoracic ratio of 56%, with a double right cardiac silhouette produced by a markedly enlarged left atrium.

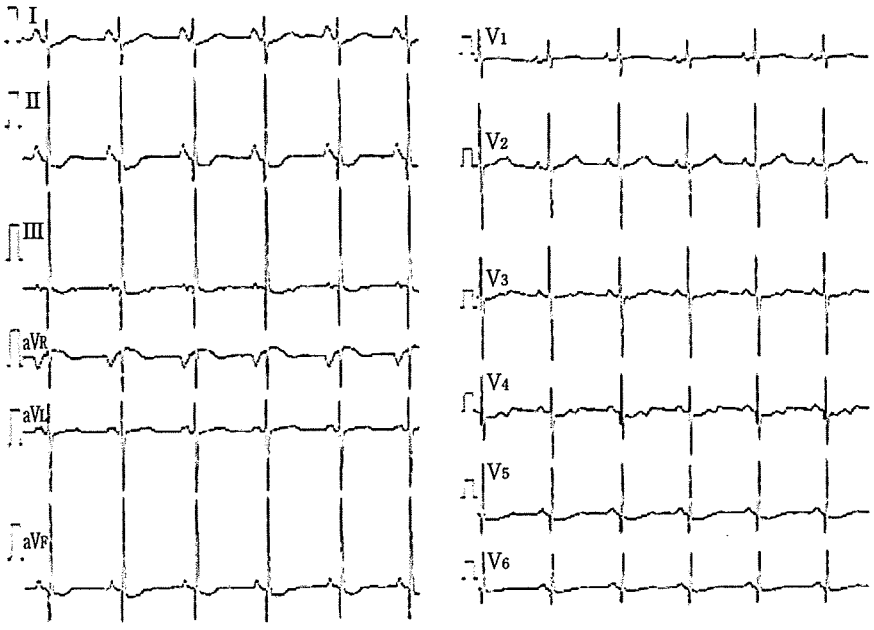

Fig. 1B Electrocardiogram shows left and right atrial enlargement, ST-segment depression, and low-voltage T waves in the inferior and lateral leads.

symptoms of cough, dyspnea on exertion, and hepatomegaly. At the age of 2 years 8 months, a bout of pneumonia led to chest radiography, which revealed cardiomegaly. Echocardiography suggested the diagnosis of RCM. At the time of referral, she was being treated with diuretics, β-blocking agents, angiotensin-converting enzyme inhibitors, isosorbide dinitrate, and aspirin. On physical examination, height was 92.8 cm, weight was 12.2 kg, systolic blood pressure was 92 mm Hg, and pulse was 78 beats per minute. No abnormal heart sounds were detected, and no significant heart murmur was audible. The liver edge was palpable 3 to 4 cm below the right costal margin, and the spleen was palpable 2 cm below the left costal margin. The plasma level of BNP was markedly elevated to 1,290 pg/mL. Chest radiography showed cardiomegaly (cardiothoracic ratio, 56%), a double silhouette along the right cardiac border indicating left atrial enlargement, and mild pulmonary congestion (**Fig. 1**