is unclear. To verify this finding, more long-term follow-up studies are needed.

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Quantitative evaluation of the changes in plasma concentrations of cardiac natriuretic peptide before and after transcatheter closure of atrial septal defect

H Muta, M Ishii, Y Maeno, T Akagi and H Kato

Department of Pediatrics, Kurume University School of Medicine, Kurume, Japan

Muta H, Ishii M, Maeno Y, Akagi T, Kato H. Quantitative evaluation of the changes in plasma concentrations of cardiac natriuretic peptide before and after transcatheter closure of atrial septal defect. Acta Pædiatr 2002; 91: 649–652. Stockholm. ISSN 0803-5253

The purpose of this study was to investigate the changes in plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in patients with atrial septal defect (ASD) during transcatheter closure of defects. The plasma concentrations of ANP and BNP were obtained from 14 patients with ASD at before closure, and at 5 min, 24 h, 1 mo and 3 mo after transcatheter ASD closure using an Amplatzer septal occluder. Ten healthy children aged 6–18 y were studied as controls. All ASDs were successfully closed. Compared with control values (mean ± SD, 17 ± 6.8 ng l^{-1}), ANP concentrations before closure were significantly elevated (24 ± 9.8 ng l^{-1}, $p < 0.05$). ANP concentrations increased significantly at 5 min after closure (34 ± 18 ng l^{-1}, $p < 0.05$) compared with preclosure concentrations. At 24 h after closure, the concentrations decreased to values not different from control values (19 ± 11 ng l^{-1}, p = ns). BNP levels before closure (19 ± 9.9 ng l^{-1}) were also elevated significantly compared with control values (12 ± 4.9 ng l^{-1}, $p < 0.05$). BNP concentrations increased significantly at 5 min after closure (23 ± 14 ng l^{-1}, $p < 0.05$) compared with preclosure concentrations. ANP values at 24 h were lower than at 5 min after closure, whereas BNP values were higher (32 ± 11 ng l^{-1}, $p < 0.05$). As with ANP, the concentrations gradually decreased to values not different from control values at 3 mo after the procedure (12 ± 6.3 ng l^{-1}, p = ns).

Conclusion: Plasma concentrations of ANP and BNP may become effective markers for evaluating changes in cardiac load after transcatheter ASD closure.

Key words: *Atrial septal defect, catheter intervention, natriuretic peptides*

M Ishii, Kurume University School of Medicine, Department of Pediatrics, 67 Asahi-machi, Kurume 830, Japan (Tel. 81 942 31 7565, fax. 81 942 38 1792, e-mail. masaishi@med.kurume-u.ac.jp)

Atrial natriuretic peptide (ANP) is a circulatory polypeptide hormone secreted mainly from the atrium, stimulated by atrial stretch, i.e. volume overloading (1). Brain natriuretic peptide (BNP) is secreted mainly from the ventricle, unlike ANP. Thus BNP is thought to be more sensitive and specific than ANP as an indicator of ventricular function (2). Atrial septal defect (ASD) is one of the most common congenital heart diseases in older children. It is characterized by volume and pressure overloading of the right side of the heart. In adult patients with ASD, plasma ANP concentrations are elevated regardless of pulmonary hypertension. In contrast, plasma BNP concentrations are elevated in proportion to the severity of pulmonary hypertension complicating ASD (1). Many studies have reported that natriuretic peptides are effective markers for evaluating cardiac situations in children with congenital heart disease (1, 3–6). A new technique using the Amplatzer septal occluder device was developed for the transcatheter closure of ASD (7). This device is simple in construction, easy to deploy, and can be withdrawn and repositioned many times. This method provides a unique condition in which pulmonary blood flow is acutely changed without the effects of cardiopulmonary bypass (8). The effect of ASD closure on ANP and BNP concentrations is unclear.

The purpose of this study was to investigate the changes in plasma concentrations of natriuretic peptides in patients with ASD before and after transcatheter closure of the defects.

Methods

Study population

A total of 14 patients with ASD (3M, 11F), aged 6–17 y (mean ± SD, 10.6 ± 3.6 y), were studied. The mean body weight was 36.4 kg (range 19–52 kg). The

diagnosis of an uncomplicated ASD was based on transthoracic echocardiography and was confirmed by cardiac catheterization. No patients had pulmonary hypertension or symptoms of heart failure before closure. There were no chromosomal abnormalities or changes in electrolytes. Ten healthy volunteers aged 6–18 y were studied as controls. Blood samples were collected from the peripheral veins in the supine position for 5 min.

Full ethical approval for this study was given by the Kurume University ethics committee. Informed consent from each patient or his or her parents was obtained prior to participation in the study.

Transcatheter atrial septal defect closure

A transcatheter ASD closure was performed using an Amplatzer septal occluder. The Amplatzer and its delivery system have been described in detail previously (7). The mean "stretched" diameter of ASD, evaluated by balloon catheter, was 15.9 mm (range 9–24 mm). The patients were intubated and placed under general anesthesia. Supplemental oxygen was not being administered during the periods of the procedure. The pulmonary to systemic flow ratio, obtained by the oximetric principles of Fick, was 2.14:1 (range 1.6:1 to 3.0:1). There were no complications, such as arrhythmia, during these procedures. There was no residual shunt in 12 patients, whereas in 2 patients there were small residual shunts immediately after the procedure. At follow-up, 24 h after ASD closure, no residual shunts were detected echocardiographically.

Sampling and assays for cardiac peptides

Blood samples were obtained from the peripheral veins in the supine position at the following measuring points: before anesthesia, and 5 min, 24 h, 1 mo and 3 mo after ASD closure. All samples were taken on awakening in the morning, except after closure periods. The samples were immediately transferred into chilled glass tubes containing disodium EDTA (1 mg ml^{-1}) and aprotinin (500 U ml^{-1}), then immediately centrifuged at 4°C, and the plasma was frozen and stored at −80°C until assayed. The plasma concentrations of ANP and BNP were measured without extraction, using specific immunoradiometric assay kits (Shionoria ANP and BNP assay kit; Shionogi Co., Osaka, Japan) as previously described (9). All assays were performed within 1 wk. The concentrations are expressed as ng l^{-1}, which can convert into 320 fmol l^{-1}.

Statistical analysis

All data are expressed as means ± SD. An analysis of variance for repeated measurement with the Student's *t*-test was used to compare the changes in natriuretic peptide concentrations after ASD closure. The unpaired *t*-test was used for comparisons between patients and controls. Values were considered to be significantly different at $p < 0.05$.

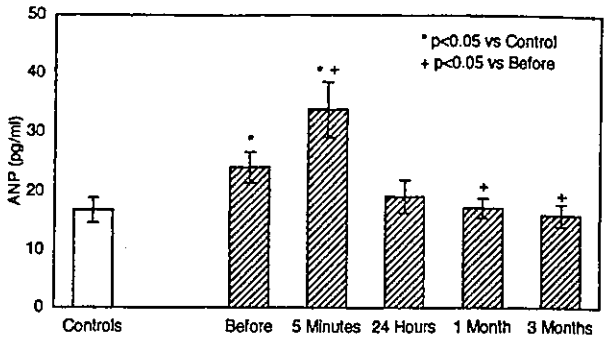

Fig. 1. Serial evaluation of atrial natriuretic peptide (ANP) in patients with transcatheter atrial septal defect (ASD) closure. Vertical bars represent standard error.

Results

The serial evaluation of ANP and BNP in children with ASD closure is presented in Figs 1 and 2. Compared with control values (17 ± 6.8 ng l^{-1}), plasma concentrations of ANP before ASD closure were significantly elevated (24 ± 9.8 ng l^{-1}, $p < 0.05$). The ANP concentrations increased significantly at 5 min after closure (34 ± 18 ng l^{-1}, $p < 0.05$) compared with preclosure concentrations. At 24 h postclosure, the ANP concentrations decreased to values not significantly different from control values (19 ± 11 ng l^{-1}, p = ns). The plasma concentrations of BNP before ASD closure were also elevated significantly compared with control values (19 ± 9.9 vs 12 ± 4.9 ng l^{-1}, $p < 0.05$). BNP concentrations also increased significantly from before to just after closure (23 ± 14 ng l^{-1}, $p < 0.05$) and continued to elevate at 24 h after closure (32 ± 11 ng l^{-1}, $p < 0.05$). As with ANP, the concentrations of BNP then gradually decreased to values not significantly

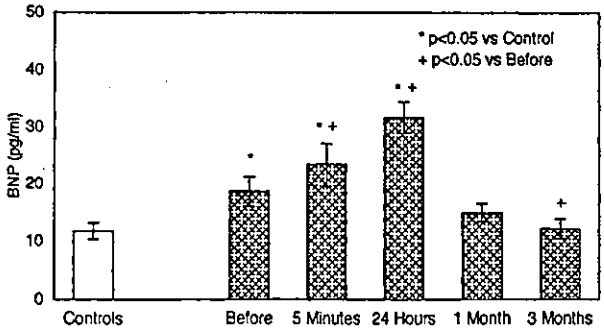

Fig. 2. Serial evaluation of brain natriuretic peptide (BNP) in patients with transcatheter atrial septal defect (ASD) closure. Vertical bars represent standard error.

different from control values at 3 mo after the procedure (12 ± 6.3 ng l^{-1}, p = ns).

Discussion

This study showed the changes in plasma natriuretic peptide concentrations before and after the ASD closure without any effects of cardiopulmonary bypass. These findings are important for understanding hemodynamics after ASD closure.

ANP is a 28 amino acid peptide mainly synthesized and secreted by the atria. It has a wide range of potent biological effects including natriuresis, vasodilatation and inhibition of the renin–angiotensin–aldosterone system (10). Previous studies have shown that increased plasma ANP concentrations in children with congenital heart disease were more prominent in those with increased pulmonary blood flow (5, 11). In clinical studies, increases in atrial pressure induced by leg raising, exercise or infusion of X-ray contrast medium brought about a rise in plasma concentrations of ANP (12). BNP is a 32 amino acid peptide predominantly secreted from the ventricles. Like ANP, it has various effects, including natriuresis, diuresis, a reduction of aldosterone, resulting in a reduction of preload, and afterload and increased stroke volume.

There are many reports of the effectiveness of evaluating cardiac situations in children with congenital heart disease (1, 3–6). However, to the authors' knowledge, little information is available regarding the changes in natriuretic peptide concentration in surgical or catheter interventions for congenital heart disease (4), especially for transcatheter ASD closure. The changes in natriuretic peptide concentration during transcatheter ASD closure may be more physiological and rapid than those during the surgical procedure, because the changes in hemodynamics, including pulmonary blood flow, can be investigated without any effects of cardiopulmonary bypass.

In the present study, the plasma ANP concentrations after the procedure significantly but transiently increased. It may be postulated that this phenomenon was caused by the reflection of atrial wall stretch due to the catheter, manipulation by the Amplatzer device or the X-ray contrast medium. This hypothesis is supported by previous studies. The atrial wall stress and stretch, rather than atrial pressure, are the predominant stimulation for ANP release (13). Waldman et al. reported that the transient elevation of ANP after percutaneous balloon mitral valvuloplasty lagged behind, returning to baseline in an exponential fashion with a half-time of 4.5 min (12). In the present study, the ANP concentrations at 1 mo after closure were similar to control values. Shaheen et al. demonstrated that the right atrial dimension regressed after ASD closure (14). So, the mechanism of ANP decreases may reflect a reduction of volume overload of right atrium. The transient elevation of BNP concentrations after ASD closure was an unexpected and interesting finding.

The changes in left and right ventricular volume were also assessed using two-dimensional echocardiography. The right ventricular volumes at 24 h after closure regressed significantly compared with preclosure (79.2 ± 25.0 vs 54.9 ± 22.4 ml m^{-2}, $p < 0.05$). The left ventricular volumes at 24 h after closure increased significantly (33.7 ± 11.6 vs 41.8 ± 12.7 ml m^{-2}, $p < 0.05$) owing to the closure of the left-to-right shunt. Yoshimura et al. described that left ventricle end-diastolic pressure significantly increased from before (10 ± 1.0 mmHg) to just after transcatheter ASD closure (17 ± 6.0 mmHg, $p < 0.05$) (15). Thus, the mechanism for the transient elevation of plasma BNP concentrations after closure may reflect both an increase in left ventricular volumes and an elevation of left ventricular end-diastolic pressure, despite a regression of the right ventricular volume overload.

The prolonged elevation of BNP concentrations after ASD closure (high at 5 min, even higher at 24 h and normal at 3 mo) was of particular interest. Differences between the structure of the atria and right ventricle, and that of the left ventricle may cause mechanistic differences. The remodeling of the left ventricle due to volume overload after the closure of the left-to-right shunt may take more time than that of the atria and right ventricle, because the left ventricle is composed almost entirely of muscle and has lower compliance.

In conclusion, the changes in plasma natriuretic peptide concentrations may reflect changes in cardiac load during transcatheter ASD closure. Plasma concentrations of ANP and BNP may become effective markers for evaluating cardiac load after catheter interventional therapy. This method is less invasive than the direct measurement using a catheter. The present study gives basic information for further quantitative assessment of the kinetics of plasma natriuretic peptides in children with congenital heart disease.

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Pediatric Cardiology

Assessment of the Ability of Myocardial Contrast Echocardiography with Harmonic Power Doppler Imaging to Identify Perfusion Abnormalities in Patients with Kawasaki Disease at Rest and During Dipyridamole Stress

M. Ishii,[1] W. Himeno,[1] M. Sawa,[2] M. Iemura,[1] J. Furui,[1] H. Muta,[1] Y. Sugahara,[1] K. Egami,[1] T. Akagi,[1] M. Ishibashi,[3] H. Kato[1]

[1]Department of Pediatrics and the Cardiovascular Research Institute, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830, Japan

[2]Agilent Technologies

[3]Department of Radiology, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830, Japan.

Abstract. The aim of our study was to assess the ability of myocardial contrast echocardiography (MCE) with harmonic power Doppler imaging (HPDI) to identify perfusion abnormalities in patients with Kawasaki disease at rest and during pharmacological stress imaging with dipyridamole. Results were compared with those of ^{99m}Tc-tetrofosmin single-photon emission computed tomography (SPECT) imaging as the clinical reference standard. MCE with HPDI was performed on 20 patients with a history of Kawasaki disease. Images were obtained at baseline and during dipyridamole infusion (0.56 mg kg^{-1}) in the apical two- and four-chamber views. Myocardial opacification suitable for the analysis was obtained in all patients. Nine patients with stenotic lesions had a reversible defect after dipyridamole infusion detected by both MCE with HPDI and SPECT, and 3 patients with a history of myocardial infarction had a partially or completely irreversible defect detected by both methods. Three patients with coronary aneurysm without stenotic lesion, 4 patients with regressed coronary aneurysm, and 2 patients with normal coronary artery in acute phase also had normal perfusion at rest and after pharmacological stress by both methods. A 96% concordance ($\kappa = 0.87$) was obtained when comparing the respective segmental perfusion scores using the two methods at baseline, and an 86% concordance ($\kappa = 0.81$) was obtained at postdipyridamole infusion. After combining baseline and postdipyridamole images, each segment was labeled as having normal perfusion, irreversible defects, or reversible defects. Using these classifications, concordance for the two methods was 92% ($\kappa = 0.87$). MCE with HPDI is a safe and feasible method by which to detect asymptomatic ischemia due to severe stenotic lesion, and it may be an important addition to the modalities used to identify patients at risk for myocardial infarction as a complication of Kawasaki disease.

Key words: Kawasaki disease — Myocardial contrast echocardiography — Harmonic power Doppler imaging — Ischemic heart disease

Although objective evaluation of myocardial ischemia and its severity is critical for patients with coronary artery disease caused by Kawasaki disease (KD), and especially for those with stenotic lesions, the conventional methods in current use for this evaluation have limitations [5]. Although coronary angiography allows for the accurate assessment of coronary involvement, consecutive and quantitative observation of ischemic diseases is often difficult [5]. Recently, the development of microbubbles, harmonic power Doppler imaging (HPDI), and an understanding of the interaction between microbubbles and ultrasound have made it possible to study myocardial perfusion with myocardial contrast echocardiography (MCE) using venous contrast agents [3, 6]. This constitutes a new method for noninvasively assessing myocardial perfusion. However, it is well-known that the resulting perfusion may be normal even in the presence of a severe coronary stenosis, a

Correspondence to: M. Ishii; *email:* masaishi@med.kurume-u.uc.jp

fact that serves as the basis for pharmacological stress imaging. Therefore, this study was undertaken to assess the ability of MCE with HPDI to identify perfusion abnormalities in patients with KD at rest and during pharmacological stress imaging with dipyridamole. Results were compared with those of ^{99m}Tc-tetrofosmin single-photon emission computed tomography (SPECT) imaging, which has emerged as the clinical reference standard for perfusion imaging [2].

Methods

Patients and Study Protocol

Twenty patients, 18 males and 2 females aged 3 to 22 years, were studied. All patients had a history of KD. Fourteen patients had coronary artery lesions, 9 patients had stenotic lesions, and 3 patients had a history of myocardial infarction. Four patients had regressed coronary aneurysm and 2 patients had normal coronary artery in the acute phase, but they complained of chest pain during the follow-up period. The clinical charactereristics of the patients are summarized in Table 1. Full ethical approval of the protocol of this study was given by the Kurume University ethics committee. We obtained informed consent from each patient or his or her parents prior to participation in the study. In all patients, MCE with HPDI was performed on the same day as the coronary angiography. The SPECT was performed 2 days after the MCE. There were no clinical events between the two studies in any of the patients. Data were acquired at baseline and after intravenous infusion of 0.56 mg kg^{-1} of dipyridamole over 4 minutes [2].

Myocardial Contrast Echocardiography

The contrast agent used in this study was Levovist (Schering AG, Berlin), a suspension of monosaccharide (galactose) microparticles in sterile water. On the basis of a previous study, we used a concentration of 300 mg/ml [1]. Regarding infusion rate, we started with 1 ml/min and a volume of 3 ml. Contrast administration was performed both at baseline and during drug-induced hyperemia. Image acquisition in the apical two- and four-chamber views was begun just before injection of contrast and continued until contrast effect in the myocardium had dissipated. MCE with HPDI was performed with a broad-band harmonic transducer (Sonos 5500, Agilent Technologies, Inc., CA, USA), transmitting and receiving at mean frequencies of 1.8 and 3.6 MHz, respectively. The dynamic range of this system is 40 dB. The mechanical index was set as high as possible to increase microbubble destruction [3]. A trigger flash MCE with HPDI mode was used in which ultrasound was transmitted by an imaging trigger gated to the T wave of the electrocardiogram every fourth cardiac cycle. End systolic triggering was used because the myocardial wall segments are thicker and the left ventricular cavity size is smaller, resulting in less contrast attenuation.

Single-Photon Emission Computed Tomography

^{99m}Tc-tetrofosmin SPECT was performed with a rotating gamma camera (E-CAM, Sienens, Berlin, Germany) equipped with an all-purpose parallel hole collimator. Redistribution images were obtained 3 or 4 hours after pharmacologic stress, according to the method used in our previous study [2].

Image Interpretation

MCE with HPDI was evaluated in blinded fashion by two observers (M.I. and W.H.). Each apical view was divided into five segments (Fig. 1), and myocardial perfusion was graded as absent, patchy, or full. During dypiridamole-induced hyperemia, the persistence of absent myocardial opacification was interpreted as an irreversible defect, whereas any decrease in perfusion grade was interpreted as a reversible defect. In addition, a partially irreversible defect was defined as a combination of a reversible defect and a fixed defect. MCE with HPDI observers were blinded to the clinical history and SPECT data on the subjects. MCE with HPDI was interpreted independently for interobserver and intraobserver variability in all 10 subjects. Horizontal and vertical long-axis views by SPECT imaging were interpreted to evaluate the myocardial segments that corresponded most closely to the echocardiographic segments.

Statistical Analysis

Concordance between MCE with HPDI and ^{99m}Tc-tetrofosmin was determined by κ statistics [9] with κ values > 0.2 = fair, > 0.4 = moderate, > 0.6 = good, and 0.8 = excellent. Two independent observers (M.I. and W.H.), with each observer individually selecting the frames to identify normal versus abnormal perfusion and to identify reversible versus irreversible defects and having no knowledge of the results obtained by the other observer, analyzed 10 randomly selected patients at different times. When the MCE with HPDI images were analyzed in 10 randomly selected patients by the same observer (M.I.) on separate occasions, the observer identified normal versus abnormal perfusion and reversible versus irreversible defects. The time period between intraobserver interpretations ranged from 1 to 3 months.

Results

Myocardial opacification suitable for analysis was obtained in all patients by MCE with HPDI under the conditions of rest and pharmacological stress. In all 20 patients, no adverse effects were noted with Levovist either at baseline or after dipyridamole infusion.

MCE versus SPECT

Analysis was performed in all of the 400 possible segments (10 per patient at baseline and the same number after dipyridamole infusion). Nine patients (patients 1–9) with stenotic lesions had a reversible defect after dipyridamole infusion detected by both MCE with HPDI and SPECT. One patient (patient 9) had an irreversible defect of the inferior wall detected subsequent to myocardial infarction 2 years previous to this study and had reversible defects of the apical

Table 1. Patient characteristics patent No

	Patient No									
	1	2	3	4	5	6	7	8	9	10
Age (years)	5	8	16	3	9	18	18	22	7	16
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Body weight (kg)	21	22	56	14.3	24	64	58	71	26	58
Age at onset of KD	1 year	5 years	11 months	3 months	7 years	3 years	4 years	1 year	4 years	11 months
Ischemic symptoms	Yes	No	None	None	Yes	Yes	None	None	None	None
Coronary artery lesion	LCA Total occlusion on seg. 6. LAD flowsupplied by DI RCA Total occlusion on seg. 1 PD and AV flow supplied by LCX	LCA Giant aneurysm on seg. 5 90% Stenosis on seg. 6 RCA regression	LCA Total occlusion at seg. 6 LAD flow supplied by RCA Small aneurysm on seg. 1	LCA Regression RCA 99% stenosis on seg. 2	LCA Giant aneurysm on seg. 5 with 99% stenosis on seg. 6 RCA Regression	LCA Regression RCA 99% stenosis on seg. 2	LCA Coronary aneurysm (5.4 mm) on seg. 5 with 99% stenosis on seg. 6 RCA Regression	LCA Regression RCA 99% stenosis on seg. 3	LCA Giant aneurysm on seg. 5 90% stenosis on seg. 6 Aneurysm on seg. 12 RCA Total occlusion on seg. 1 without collateral flow	LCA Giant aneurysm on seg.5 and seg. 6 RCA Total occlusion on seg. 1 without collateral flow
History of MI	None	None	None	None	None	None	None	None	Yes, 5 years	Yes, 2 years
Perfusion defects were detected by MCE (Fig. 1)	Reversible defects of seg. 3 and seg. 6	Reversible defects of seg. 3	Reversible defects of seg. 3	Reversible defects of seg. 6	Reversible defects of seg. 3	Reversible defects of seg. 7	Reversible defects of seg. 3	Reversible defects of seg. 6	Reversible defects of seg. 3; irreversible defect of seg. 6	Partially irreversible defect of seg. 6
Perfusion defects were detected by 99m Tc-tetrofosmin SPECT	Yes Reversible defect of apical and anteroseptal wall	Yes Reversible defect of apical wall	Yes Reversible defect of apical wall	Yes Reversible defect of inferior wall	Yes Reversible defect of apical wall	Yes Reversible defect of inferior wall	Yes Reversible defect of apical wall	Yes Reversible defect of inferior wall	Yes Reversible defect of apical and anteroseptal wall Irreversible defect of inferior wall	Yes Partially irreversible defect of inferior wall

Table 1. Continued

Patient No.									
11	12	13	14	15	16	17	18	19	20
12	8	19	6	4	3	17	18	15	16
Male	Male	Male	Male	Male	Female	Male	Male	Male	Male
38	22	55	30	16	13	54	58	54	54
6 months	8 years	8 years	2 years	8 months	10 months	1.3 years	11 months	10 months	10 months
None	None	None	None	None	None	None	None	None	None
LCA Giant aneurysm on seg. 5 Total occlusion of LAD on seg. 6 RCA Giant aneurysm on seg. 1	LCA Coronary aneurysm (4.8 mm) on seg. 11 (LCX) RCA Coronary aneurysm (6 mm) on seg. 1 and seg. 3	LCA Coronary aneurysm (6.2 mm) on seg. 6 RCA Regression	LCA Coronary aneurysms (4.5 mm) on seg. 5 and seg. 6 RCA Regression	LCA Regression RCA Regression	LCA Regression RCA Regression	LCA Regression RCA Normal	LCA Normal RCA Regression	LCA Normal RCA Normal	LCA Normal RCA Normal
Yes, 1 year	None	None	None	None	None	None	None	None	None
Partially irreversible defect of seg. 3	None	None	None	None	None	None	None	None	None
Yes Partially irreversible defect of apical and antero-septal wall	None	None	None	None	None	None	None	None	None

KD, Kawasaki disease; *MI*, myocardial infarction, *LAD*, left anterior descending artery; *DI*, 1st diagonal artery; *LCA*, left coronary artery; *RCA*, right coronaryartery; *SEG*, segments; *LCX*, left circumflex artery; *PD*, posterior descending coronary artery; *AV*, artoventricular node artery.

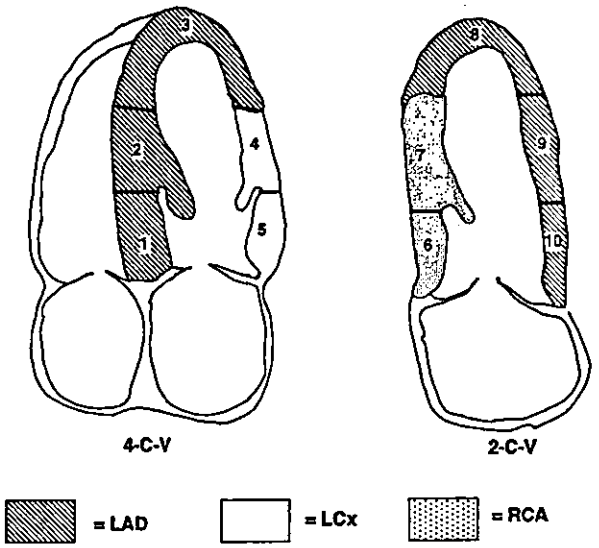

Fig. 1. Schema of segments analyzed for myocardial perfusion and the coronary artery territories to which they were assigned. 4-C-V and 2-C-V are four- and two-chamber views, respectively. *LAD*, left anterior descending territory; *LCx*, left circumflex territory; *RCA*, right coronary arterial territory.

and anteroseptal walls due to 90% stenosis of the left anterior descending coronary artery by both pharmacological stress MCE with HPDI and SPECT. The 2 patients (patients 10 and 11) with a history of myocardial infarction had a partially irreversible defect which was defined to be the combination of a reversible defect and a fixed defect. Three patients (patients 12–14) with coronary aneurysm without stenotic lesions had normal perfusion at rest and after dipyridamole detected by both MCE with HPDI and SPECT. In addition, 4 patients (patients 15–18) with regressed coronary aneurysm and 2 patients (patients 19 and 20) with normal coronary artery in the acute phase also had normal perfusion at rest and after pharmacological stress by both MCE with HPDI and SPECT. A 96% concordance ($\kappa = 0.87$) was obtained when the segmental perfusion scores of the two methods at baseline were compared. In the post-dipyridamole images, an 86% concordance ($\kappa = 0.81$) was obtained. After combining baseline and post-dipyridamole images, all segments were labeled as having normal perfusion, irreversible defects, or reversible defects. Using these classifications, the concordance for the two methods was 92% ($\kappa = 0.87$). Figure 2 shows an example of a reversible defect. A 5-year-old boy's (patient 1) MCE with HPDI and SPECT showed normal perfusion at baseline. After dipyridamole infusion, both MCE with HPDI and SPECT showed an anteroseptal and an apical perfusion defect. The apical perfusion defect was persistent, though the focus moved from base to apex. Coronary angiography showed total occlusion of the left descending coronary artery, with the coronary arterial flow supplied by the diagonal artery. Both MCE with HPDI and SPECT demonstrated that his myocardium was viable. He underwent aortocoronary bypass surgery after this study. Figure 3 illustrates examples of partially irreversible defects, which are the combination of a reversible defect and an irreversible defect, in images from a patient who had myocardial infarction due to total occlusion of the right coronary artery 14 years prior to this study (patient 10). He had a basal posterior defect in the two-chamber view that was identical on MCE with HPDI and SPECT. His myocardial perfusion defect partially increased after dipyridamole infusion. Coronary angiography showed total occlusion of the right coronary artery without development of collateral vessels. Figure 4 demonstrates normal perfusion at rest and after dipyridamole infusion in patient 20, who had normal coronary arteries after KD.

Observer Variability

The intraobserver agreement was 96% ($\kappa = 0.93$) in identifying normal versus abnormal perfusion and 90% ($\kappa = 0.88$) in identifying reversible versus irreversible defects. The interobserver variability was 95% and 92% for the two observers.

Discussion

This study demonstrates that MCE with HPDI, with the use of an intravenous contrast agent, can detect myocardial perfusion in patients with KD at rest and during pharmacological stress. The locations of these perfusion abnormalities and their physiological relevance provided by this method are similar to those provided by SPECT.

Advantage of MCE with HPDI for KD Patients

Patients with KD who develop myocardial infarction are usually asymptomatic before the event; thus, it is crucial that patients at risk be identified and followed closely (noninvasively if possible) so that appropriate catheter and surgical interventions can be undertaken before infarction or sudden death [5]. However, the conventional methods in current use for this evaluation have limitations for detecting coronary stenosis. Although two-dimensional echocardiography can assist in detecting coronary aneurysms, its use in the evaluation of stenotic lesions is not satisfactory. Coronary angiography allows accurate assessment of coronary artery involvement, but repeated evaluation is often difficult because this procedure is invasive.

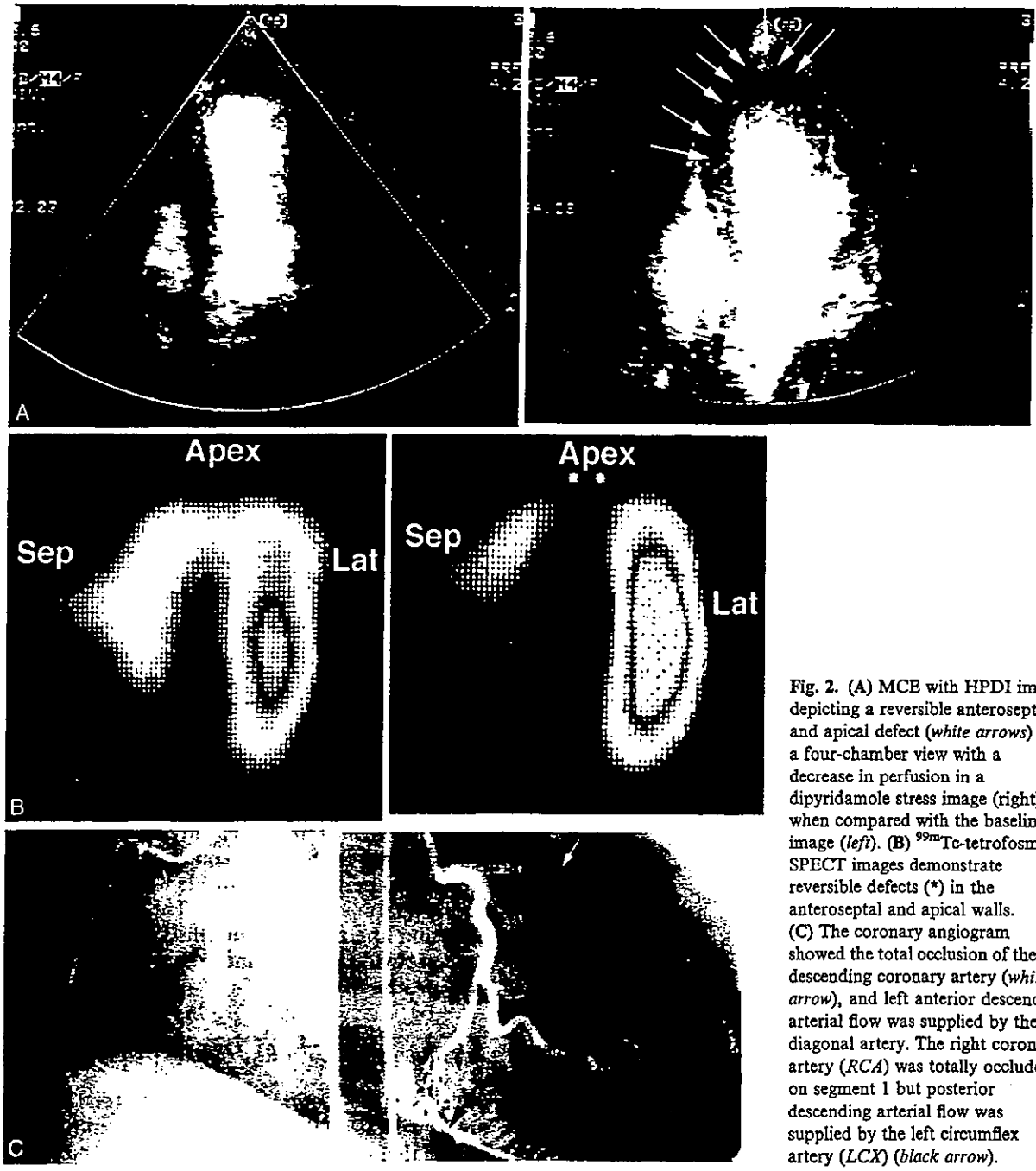

Fig. 2. (A) MCE with HPDI image depicting a reversible anteroseptal and apical defect (*white arrows*) in a four-chamber view with a decrease in perfusion in a dipyridamole stress image (right) when compared with the baseline image (*left*). (B) ^{99m}Tc-tetrofosmin SPECT images demonstrate reversible defects (*) in the anteroseptal and apical walls. (C) The coronary angiogram showed the total occlusion of the left descending coronary artery (*white arrow*), and left anterior descending arterial flow was supplied by the 1st diagonal artery. The right coronary artery (*RCA*) was totally occluded on segment 1 but posterior descending arterial flow was supplied by the left circumflex artery (*LCX*) (*black arrow*).

Myocardial SPECT with dipyridamole infusion is a safe and accurate diagnostic method for identifying coronary stenosis in children with KD [2]. However, use of this technique is limited because it requires the injection of radioisotopes. It is also time-consuming and expensive. MCE uses microbubbles as contrast agents, and these microbubbles scatter ultrasound during their transit through the coronary microcirculation [7, 8]. The assessment of myocardial perfusion in patients with KD through the use of this MCE technique has been limited by the need to inject microbubbles directly into the coronary arteries [7, 8]. The recent development of microbubbles, HPDI, and an understanding of the interaction between microbubbles and ultrasound has made it possible to study myocardial perfusion with MCE using venous contrast agents [3, 6]. This constitutes a new method for noninvasively assessing myocardial perfusion. The

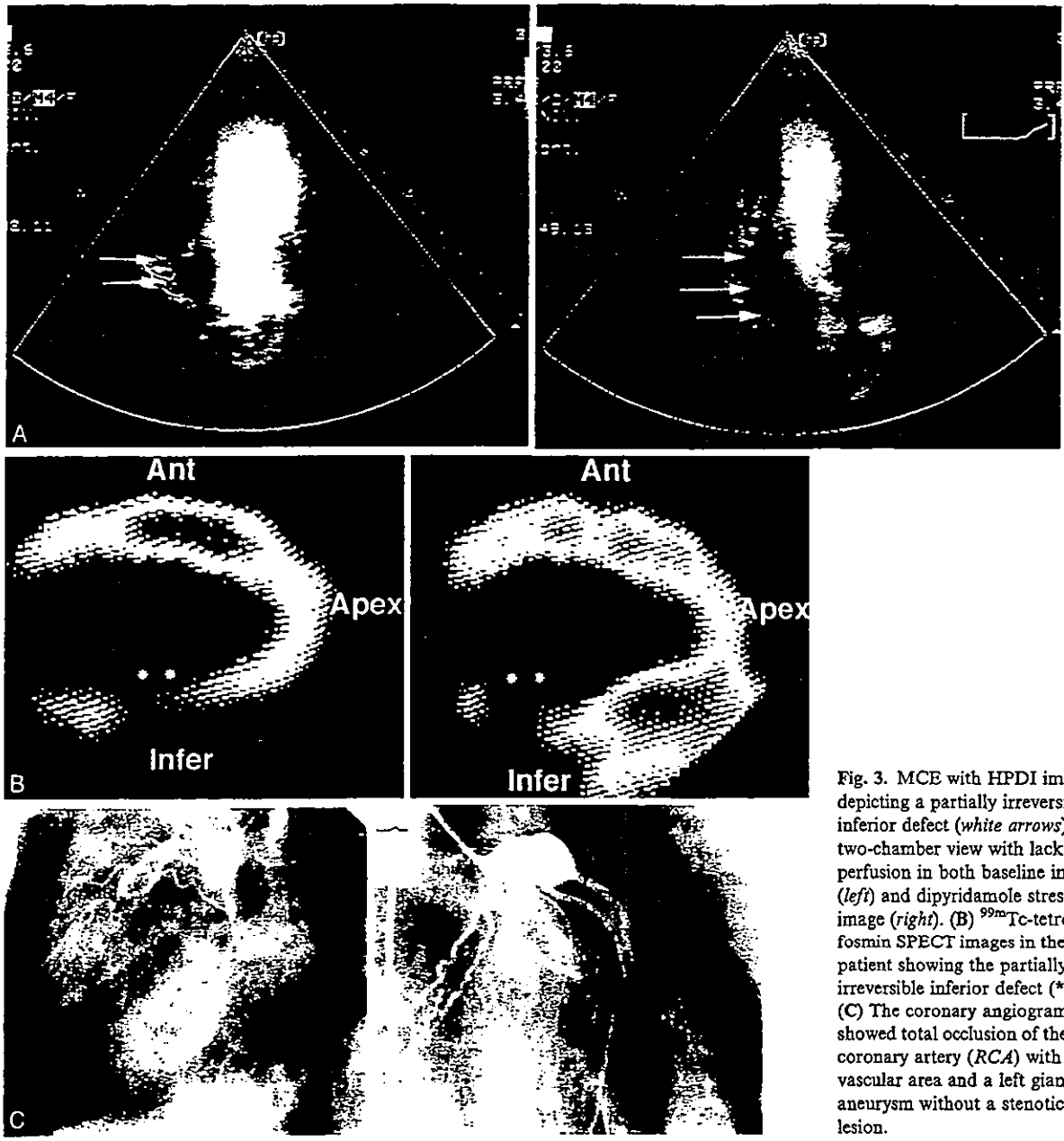

Fig. 3. MCE with HPDI image depicting a partially irreversible inferior defect (*white arrows*) in a two-chamber view with lack of perfusion in both baseline image (*left*) and dipyridamole stress image (*right*). (B) ^{99m}Tc-tetrofosmin SPECT images in the same patient showing the partially irreversible inferior defect (*). (C) The coronary angiogram showed total occlusion of the right coronary artery (*RCA*) with a vascular area and a left giant aneurysm without a stenotic lesion.

advantages of MCE with HPDI compared to other methods are that it is noninvasive, provides immediate information, can be performed on infants and young children (even at the acute phase), and involves no radiation exposure [2, 3, 6]. In addition, MCE with HPDI can be performed on patients with KD at the bedside or in the outpatient clinic. This MCE with HPDI technique may also be useful for serially following KD patients in order to identify worsening coronary artery lesion, especially developing severe coronary artery stenosis.

Mechanism of Perfusion Detection by HPDI

HPDI, like conventional Doppler velocity imaging, transmits a packet of ultrasound pulses along each scan line and uses an autocorrelator to compare differences in the received signals [4]. HPDI displays the amplitude of the received signals, which reflects the number of scatterers. Two mechanisms have been proposed for the detection of myocardial perfusion by MCE with HPDI. One, termed "stimulated acoustic emission," postulates that microbubble de-

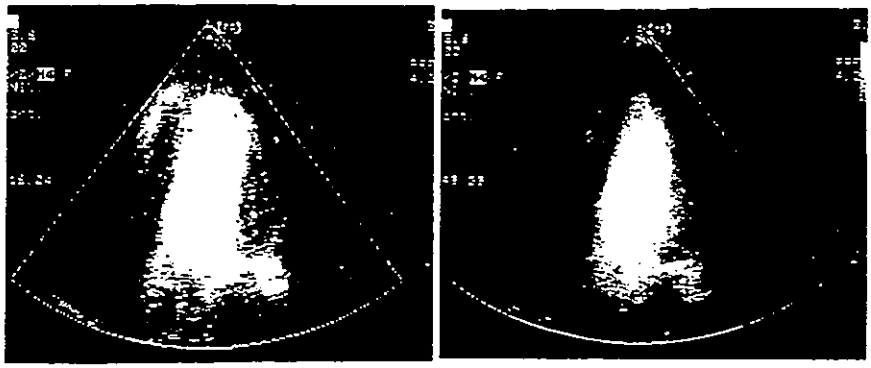

Fig. 4. MCE with HPDI image of patient with normal coronary artery after Kawasaki disease demonstrated normal perfusion at rest (*left*) and after dipyridamole stress (*right*)

struction produces an acoustic energy that results in HPDI signals. Second, and more likely, is that microbubble destruction results in a decrease in backscattered intensity and a change in phase between pulses; the autocorrelator interprets this as motion and therefore displays a signal. In either case, microbubble destruction is necessary for HPDI to detect myocardial perfusion.

Study Limitation

Digital acquisition of HPDI should lend itself to quantitative analysis, which may be more accurate in distinguishing normal perfusion from mild defects. Moreover, quantitative analysis offers the potential to actually measure flow reserve ratio noninvasively. Unfortunately, quantification of the digital HPDI signal is not available on the instrument used in this study. We did not use off-line quantification of videotape because that technique is not readily applied to clinical practice due to time constraints, and it has the potential for loss of data quality and errors in extrapolating signal intensity from the color bar to the myocardial regions. Furthermore, the classification of defects is not an all-or-none phenomenon. Defects may be predominantly fixed with some reversibility at the edge in two of three patients with a history of myocardial infarction. We defined this phenomenon as a partially irreversible defect. The evolution of quantitative techniques may allow more precise classification of irreversible and reversible defects.

Conclusions

The results of this study show that it is possible to detect coronary artery stenotic lesion due to KD by MCE with HPDI through the use of venous injections of microbubbles. We conclude that MCE with HPDI is safe and feasible, and it may be an important addition to the modalities used to identify children at risk for myocardial ischemia caused by KD.

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Circ J 2003; **67**: 112–115

Incidence and Clinical Features of Asymptomatic Atrial Septal Defect in School Children Diagnosed by Heart Disease Screening

Hiromi Muta, MD; Teiji Akagi, MD; Kimiyasu Egami, MD; Jun Furui, MD; Yoko Sugahara, MD; Masahiro Ishii, MD; Toyojiro Matsuishi, MD

The purpose of this study was to investigate the incidence and clinical features of atrial septal defect (ASD) in school children in Japan who were diagnosed by heart disease screening. From 1989 to 1998, a questionnaire, electrocardiography (ECG) and phonocardiogram were obtained from school children when they entered their first year of elementary school (n=86,142) or junior high school (n=80,632). In this program, 33 asymptomatic ASD patients were newly diagnosed (0.020%). The ECG findings showed incomplete right bundle-branch block (79%), right axis deviation (55%), and right ventricular hypertrophy (9%). An ejection systolic murmur was audible in 30 patients (94%) and mid-diastolic murmur in 10 patients (30%). Thirty patients (90%) showed fixed split of second heart sound. Using echocardiography or catheter observation, 31 patients (94%) were judged to require closure of the ASD. Although the medical care is widely available in Japan, undetected ASD patients were not rare and importantly, most of them required closure of the defect even if they were asymptomatic. (*Circ J* 2003; **67**: 112–115)

Key Words: Atrial septal defect; School children; Screening program

Atrial septal defect (ASD) is one of the most common congenital heart diseases among older children and most childhood cases are diagnosed because of heart murmur or cardiomegaly detected on chest X-ray. However, even in the current era, ASD may not be diagnosed until adulthood when there are complications of congestive heart failure or atrial arrhythmia. In Japan, nationwide heart disease screening for school children has been carried out since 1973 and children in their first year of elementary school (7 years old) or junior high school (13 years old) are required by law to be screened. The most common and significant organic heart disease diagnosed in this program is ASD.

Using data from this mass-screening program, we set out to clarify the incidence and clinical features of the patients newly diagnosed by the screening program as having ASD.

Methods

From 1989 to 1998, almost all school children in the southern area of Fukuoka prefecture and the northern and eastern areas of Saga prefecture were screened (Fig 1) when they entered either elementary school (age 6–7 years, n=86,142) or junior high school (age 12–13 years, n=80,632). The program applied only to the Kurume area.

In the preliminary screening, students were given a questionnaire to be completed at home by their parents, and they underwent electrocardiography (ECG) with 4 simplified leads (I, aVF, V1, V6), and phonocardiography (PCG) at the second left intercostal space and apex. The questionnaire sought details of the student's past history of heart diseases, including Kawasaki disease, cardiac symptoms, and family history (Table 1). The ECGs were analyzed by computer and reviewed by pediatric cardiologists. To standardize the judgment of the ECG, there was a guideline for secondary screening[1] The PCGs were also reviewed by pediatric cardiologists. Nearly 10% of students had at least one suspicious finding of heart disease that required secondary screening, which comprised physical examination, 12-lead ECG, chest X-ray and color-flow Doppler echocardiography (if needed), all performed by pediatric cardiologists. The children who were suspected to have heart disease or who needed other precise examinations were recommended for tertiary examination. We followed these patients until December 2001 or the time of closure of ASD (mean follow-up period, 4.8 years).

Statistical Analysis

The chi-square test was used to determine diagnostic incidence. A value of $p<0.05$ was considered statistically significant.

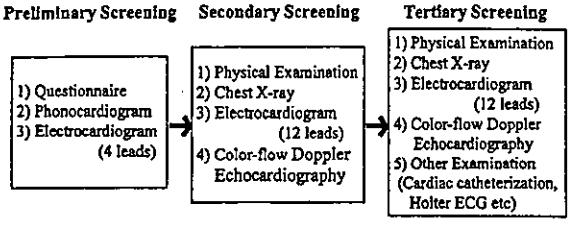

Fig 1. Program of heart disease screening for school children.

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Department of Pediatrics, Kurume University School of Medicine, Kurume, Japan

Mailing address: Hiromi Muta, MD, Department of Pediatrics, Kurume University, 67 Asahi-machi, Kurume 830-0011, Japan. E-mail: QZE05346@nifty.com

Table 1 Questionnaire in Preliminary Screening

1. *Have you ever been diagnosed with any heart disease?*
   How old were you when it was first diagnosed?
   What diseases have you been diagnosed with?
   What management have you received?
2. *Have you ever diagnosed diseases such as chorea, rheumatic fever, Kawasaki disease, hypertension, sepsis, thyroid disease, or arthritis?*
3. *Have you had any of the following symptoms: fatigue, palpitation, shortness of breath, chest oppression, syncope or faintness?*
4. *Do you have any consanguineous who had sudden death younger than 40 years old?*

Table 2 Patient's Data

Case no.	Sex	Age (Years)	IRBBB	RAD	RVH	RAE	ESM	FS	MDM	Diameter (mm)	Surgical indication
1	Male	7	Rsr	Yes	No	No	Yes	Yes	Yes	9	Yes
2	Male	6	rsR	Yes	No	No	Yes	Yes	Yes	25	Yes
3	Female	13	rsR	Yes	No	No	Yes	Yes	No	10	Yes
4	Male	7	rsR	Yes	No	No	Yes	Yes	No	6	Yes
5	Female	6	–	No	No	No	Yes	Yes	No	5	Yes
6	Female	7	Rsr	No	No	No	Yes	Yes	No	20	Yes
7	Female	6	–	Yes	No	No	Yes	Yes	No	12	Yes
8	Female	6	rsR	No	Yes	No	Yes	Yes	No	6	Yes
9	Female	13	–	No	No	Yes	Yes	Yes	Yes	20	Yes
10	Female	7	rsR	Yes	No	No	Yes	Yes	No	6	Yes
11	Female	13	Rsr	Yes	No	No	No	Yes	No	11	Yes
12	Male	12	rsR	Yes	No	No	Yes	Yes	Yes	12	Yes
13	Male	7	rsR	No	No	No	Yes	Yes	No	15	Yes
14	Male	13	Rsr	No	No	No	Yes	Yes	Yes	15	Yes
15	Female	12	rsR	No	No	No	Yes	Yes	Yes	14	Yes
16	Male	12	rsR	Yes	No	No	Yes	Yes	Yes	23	Yes
17	Male	12	Rsr	No	No	No	No	Yes	No	13	Yes
18	Male	7	rsR	Yes	Yes	Yes	Yes	Yes	No	8	Yes
19	Male	6	rsR	Yes	No	No	Yes	Yes	Yes	12	Yes
20	Male	7	rsR	Yes	No	No	Yes	No	No	12	Yes
21	Male	7	rsR	No	No	No	Yes	Yes	No	10	Yes
22	Male	7	rsR	Yes	No	No	Yes	Yes	Yes	20	Yes
23	Male	6	–	Yes	No	No	Yes	Yes	No	10	Yes
24	Male	13	Rsr	No	No	No	Yes	Yes	Yes	5	No
25	Female	13	rsR	Yes	No	Yes	Yes	Yes	No	17	Yes
26	Male	6	rsR	Yes	No	No	Yes	Yes	No	3	Yes
27	Female	6	rsR	No	Yes	No	Yes	No	No	11	Yes
28	Male	13	Rsr	Yes	No	No	No	Yes	No	8	Yes
29	Male	13	rsR	No	No	No	Yes	No	No	15	Yes
30	Male	13	–	Yes	No	No	Yes	Yes	No	4	No
31	Female	7	rsR	No	No	No	Yes	Yes	No	21	Yes
32	Male	7	–	No	No	No	Yes	Yes	No	9	Yes
33	Female	13	–	No	No	No	Yes	Yes	No	3	No

IRBBB, incomplete right bundle-branch block; RAD, right axis deviation; RVH, right ventricular hypertrophy; RAE, right atrial enlargement; ESM, ejection systolic murmur; FS, fixed split of second heart sound; MDM, mid-diastolic murmur.

Results

A summary of the results is shown in Table 2.

Patient Profiles

The compliance rate of screened children was 98.7% (166,774/168,971) and in this study period, 33 patients with ASD (20 males, 13 females, 0.020% of screened children) were newly diagnosed. The incidence of those entering elementary school (0.023%) was significantly higher than those entering junior high school (0.016%, $p<0.05$). Among these patients, one case of ASD was complicated by partial anomalous pulmonary venous connection, another with left-sided superior vena cava, and one with Wolff-Parkinson-White syndrome. All patients had ostium secundum ASD and all were completely asymptomatic without a family history of congenital heart disease.

ECG findings

At the time of diagnosis, incomplete right bundle-branch block (IRBBB) was observed in 26 patients (79%), right axis deviation in 18 patients (55%), right ventricular hypertrophy in 3 patients (9%), and right atrial enlargement in 2 patients (6%). All patients showed normal sinus rhythm and 4 (12%) had no significant ECG abnormalities. There were no significant differences in the ECG findings of the elementary school children and those of the junior high school children.

Auscultation Findings

An ejection systolic murmur at the second left intercostal space was audible in 30 patients (91%), and a mid-diastolic murmur at the lower left sternal border was audible in 10 (30%) at the second screening. Of those 30 patients, 25 (83.3%) had already had the murmur detected in the first

Table 3 The Goals of The Heart Disease Screening Program for School Children in Japan

1. *To find out the children with heart disease.*
2. *To receive the precise diagnosis and judge the severity of disease.*
3. *To manage children with heart disease in school life including after operation and prevent sudden death.*
4. *To follow up these patients after school age.*

screening, and 6 patients (18%) had noted the presence of a heart murmur before the screening. In 4 of them, the murmur had been diagnosed as innocent by their family doctor and 2 of them had refused further precise examinations. The 30 patients (91%) had a typical wide and fixed split of the second heart sound, and in the second screening, the intensity of the heart murmur as classified by Levine ranged from I through III. A significant heart murmur could not found in 3 patients (6%) and in 2 of them, the ASD was greater than 10mm. Case 11 had IRBBB and right axis deviation detected in the first screening and her ratio of pulmonary to systemic blood flow (Qp/Qs) was 1.7. Case 17 had IRBBB and fixed split detected in the first screening and 1 year after screening, an ejection systolic murmur was audible with an intensity of II/VI; his Qp/Qs was 2.5.

Echocardiographic Findings

The size of the ASD was measured by transthoracic echocardiography from the subxyphoid long- and short-axis views. The diameter of the defects ranged from 3 to 30mm, with a mean of 11.8±5.9mm.

Treatment

On the basis of echocardiography or catheter observation, a large left-to-right shunt (Qp/Qs >1.5) or enlargement of the right atrium and ventricle was taken as an indication that the ASD should be closed and 31 patients (94%) were judged positive. At screening, 5 cases of ASD had a diameter less than 5mm and of them the defects had grown in 2 cases. Case 5, a 6-year-old girl at initial screening, had a left-sided superior vena cava and 6 years later, echocardiography showed enlargement of the right atrium and ventricle, and cardiac catheterization showed a Qp/Qs of 1.7. Case 26, which was the same as case 5, had cardiac catheterization 7 years after screening, which revealed a Qp/Qs of 1.96; the diameter of the ASD at operation was 10×15mm. Surgical or transcatheter closure of the ASD was performed in 18 patients (58%) and all have had a good clinical course since then.

Discussion

In Japan, heart disease screening for school children has been performed nationally since 1973; its goals are outlined in Table3. Previous studies have reported that the diagnostic incidence of ASD found by heart disease screening in school children ranges from 0.010 to 0.021%[2,3] Spontaneous closure of an isolated ASD has been reported in 17–84% of infants and documented at ages 2–8 years.[4–6] However, if the defect persists until school age, it will not close. There is no obvious advantage in delaying repair beyond the teenage years and, in fact, such delay may increase the risk of diseases, such as supraventricular tachycardia, and ventricular dysfunction.[7,8] Almost all patients in this study who were detected by screening were judged to need closure of ASD and from this viewpoint, the discovery of ASD at school age by means of this program is valuable.

What is the best method of finding the patients with ASD? A questionnaire is easy and inexpensive, but its sensitivity of detection in this age group would be low because most cases of ASD are asymptomatic. ECG gives beneficial information for the diagnosis of ASD, especially IRBBB and right axis deviation, but a previous study reported that only 0.26% of patients with IRBBB also had ASD? In the present study, only 48% of patients had both IRBBB and right axis deviation and this is further complicated by the fact that 12% of those with ASD did not have any ECG findings. Therefore, screening using only ECG cannot detect all ASD patients. PCG is useful for diagnosing systolic murmur and fixed split in ASD patients, but 'noise' at the screening site is often problematic, especially when screening younger children. The use of echocardiography for the secondary screening will assist in the diagnosing of heart disease. Steinberger et al reported that clinically significant cardiac disease in childhood that can be detected only by echocardiography is not rare;[10] however, echocardiography requires greater manpower and funding.

During the follow-up period, the diameter of ASD had increased in 2 cases. At initial screening, these cases of ASD were too small and not indicated for closure, but 6–7 years later, they each had a large left-to-right shunt and were indicated for closure. Long-term follow-up is required for these tiny defects.

Conclusions

Although medical care is widely available in Japan, it is not uncommon for patients with ASD to remain undetected until school age. Significantly, most of these patients have to have their defects closed even if they were asymptomatic.

Study Limitations

First, our data relied heavily on the responses to the questionnaire regarding symptoms and younger children may not be able to articulate their symptoms clearly. Therefore, we may have underestimated the presence of symptoms. Second, echocardiography is more widely available for infant screening today, so the incidence of ASD patients newly diagnosed at school age will decrease.

Acknowledgments

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成人でみられる川崎病後遺症

菅原 洋子・石井 正浩・赤木 禎治

ポイント

▶ 川崎病は4歳以下の乳幼児に発症する疾患であるが，後遺症をもったまま成人期に移行する患者が増えている．γグロブリン治療の導入によって冠動脈瘤の発生頻度は5％以下に低下したが，いまだ完全に抑制できていない．原因不明の冠動脈瘤を伴う若年成人の虚血性心疾患をみた場合，第一に考えるべき疾患である．

川崎病は，主に4歳以下の乳幼児に好発する全身の中小動脈に起こる血管炎であり，その原因はいまだ不明である．最も重要な心血管合併症は，冠動脈病変である．そのほかに弁膜症，心筋炎，心膜炎，全身動脈病変を生じる．川崎病の最初の報告からすでに40年近く経過し，初期の症例はすでに成人期に達している．本稿では，川崎病心血管障害の自然歴と成人における川崎病心血管後遺症について述べる．

川崎病の心血管合併症

図1に当施設で経験した川崎病1,898例の心血管病変臨床スペクトラムを示す．冠動脈瘤は，全1,898例中297例(15.6％)にみられた．γグロブリン療法導入後は，5％以下にその発生頻度は減少している．急性期の冠動脈の一過性拡大は

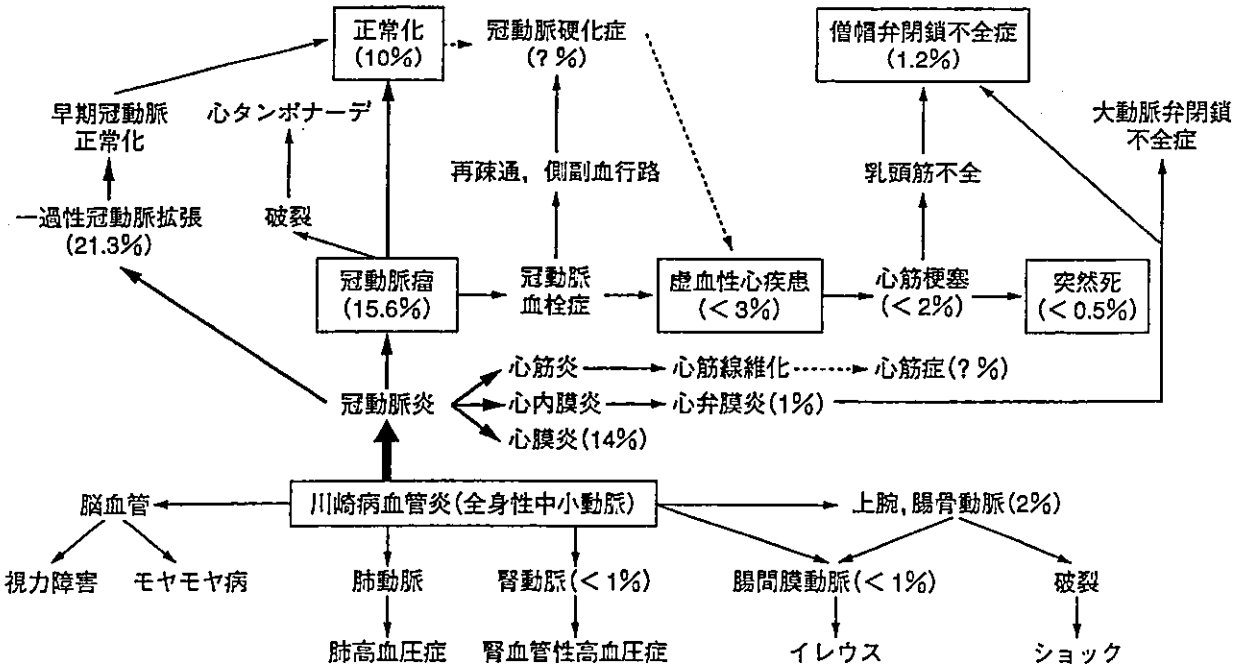

図1　川崎病心血管病変のスペクトラムと自然歴

すがはら ようこ，いしい まさひろ，あかぎ ていじ：久留米大学医学部小児科　〒830-0011 福岡県久留米市旭町67

21.3％にみられた．腋下動脈や腸骨動脈などの全身動脈の動脈瘤は21例(1.1％)にみられた．僧帽弁閉鎖不全は22例(1.2％)，大動脈閉鎖不全は4例(0.2％)であった．急性期で起こる弁膜症は弁膜炎に起因し，経過とともに数カ月～数年のうちに消退することが多いが，虚血に伴う乳頭筋不全による僧房弁閉鎖不全は軽快することは少ない．大動脈弁閉鎖不全は急性期以降に発症し，次第に進行する例もみられる．心エコー図でみられる心嚢液貯留も含めると心膜炎は14％，心筋炎は軽症のものを含めると約32％に起こっていると推測される．川崎病における心膜炎や心筋炎は，一般に軽症で後遺症として問題となることはないと考えてよい．心筋梗塞は24例に発生し，そのうち10例が死亡しており致命率は高い．

川崎病冠動脈病変の長期予後

川崎病冠動脈瘤の約50％は，発症後1～2年後で冠動脈瘤の消退(regression)を認める．残る半数は動脈瘤の残存，もしくは狭窄病変へ進展し，最終的に虚血性心疾患に進展するのは，全川崎病症例の3％程度である(図2)．冠動脈瘤から狭窄病変への進行は，発症後長期にわたって徐々に進行する．10年以上の経過をもって狭窄病変へと進行していく例も珍しくない[1]．

急性期に冠動脈病変を認めていない例や早期にregressionした例においては，遠隔期に虚血性心臓病への進行を疑わせる症状を認めることはきわめて稀である．急性期冠動脈病変を認めていない例，急性期に一過性拡大をきたした例や動脈瘤がregressionした例では，臨床上虚血性心疾患としての問題はないと考えられる．しかしながら，病理学的には退縮した血管病変では血管内膜の明らかな肥厚が認められ，長期的には成人期の動脈硬化病変のリスクファクターとなる可能性もあり，長期フォローアップによる検討が必要と思われる．

川崎病冠動脈狭窄病変に対する治療は，冠動脈バイパス術の成績向上とカテーテルインターベンションの導入により大きく変化してきている[2]．

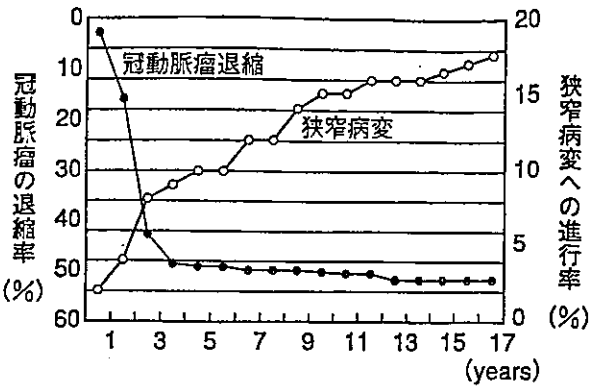

図2　冠動脈病変の長期予後（文献1より）

カテーテル治療としては，バルーンによる冠動脈形成術に加え，ロータブレーターやステントといった新しいデバイスで外科治療と同様の治療効果が期待されるに至っている．川崎病冠動脈狭窄病変が進行性の病変であること，成人の動脈硬化性病変に比べ石灰化が強く通常のバルーンでは拡大できない場合が多いことなどから，カテーテル治療の適応や手技選択など，今後経験を増やして解決していくべき分野が多く残されている．

川崎病血管炎は動脈硬化のリスク因子か

川崎病血管炎が動脈硬化の危険因子であり，早期動脈硬化に進展する可能性が指摘されている．動脈瘤がregressionする過程には，中膜平滑筋の強い増殖による内膜の肥厚が大きな因子となっている．消退した動脈瘤のみならず，残存する動脈瘤にも同じような内膜肥厚や血栓の器質化による内膜の肥厚が認められる．数年経過した動脈瘤は動脈瘤壁に石灰化をきたすが，これらは広い意味の動脈硬化所見である．

これら退縮した冠動脈病変に，アセチルコリンやイソソルビドを用いて血管内皮機能を検討してみると，急性期の冠動脈病変が直径4 mm未満であった場合には，遠隔期における血管内皮機能は健常児と有意差を認めなかったが，急性期の冠動脈病変が4 mm以上の部位では，退縮した後にも血管内皮機能の異常が確認された[3]．退縮した部位を血管内エコーで検討すると，急性期の冠

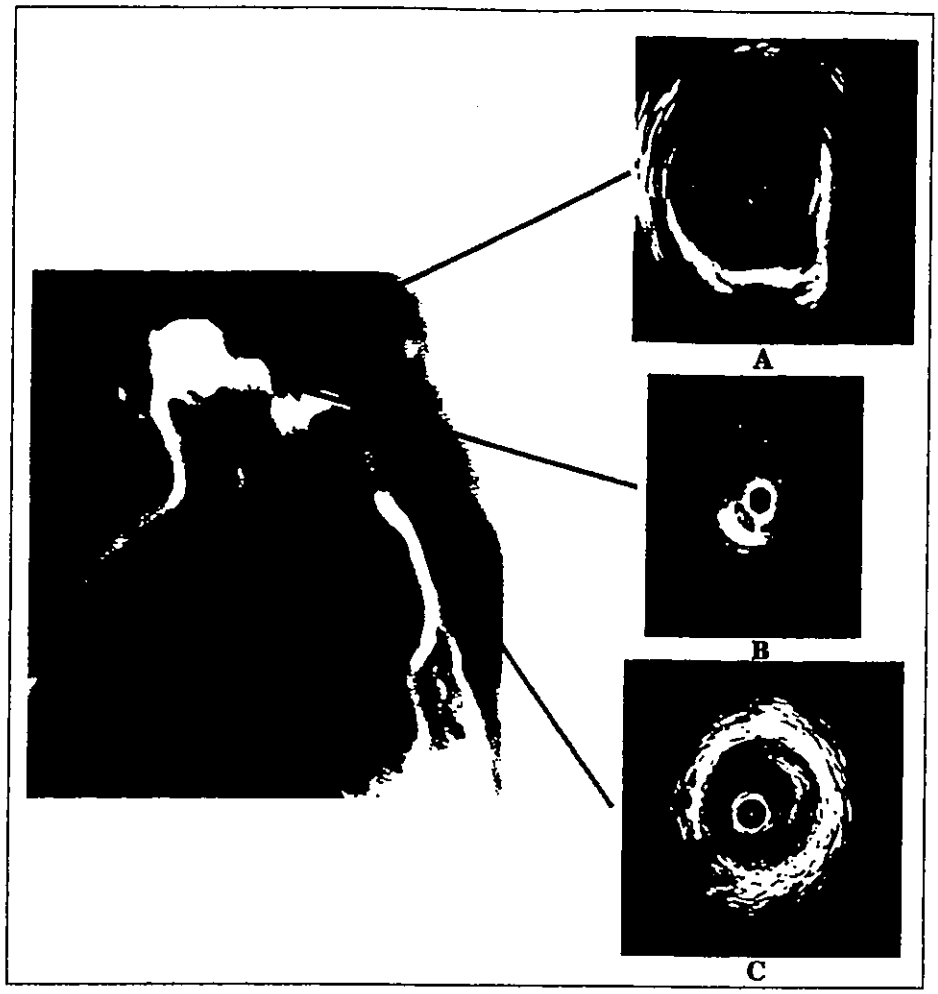

図3　川崎病冠動脈病変の血管内エコー像
A：冠動脈瘤，B：冠動脈狭窄部，C：冠動脈瘤退縮部

動脈病変が4mm以上の部位では，退縮した部位に血管内膜および中膜の肥厚を認めた．健常児や急性期の冠動脈病変が直径4mm未満であった場合には，このような血管内中膜の肥厚所見は認められず，川崎病血管病変の遠隔期所見として重要な所見と思われる(図3)．剖検組織を用いた最近の免疫組織学的検討では，肥厚した血管内膜には同時に血管新生も発現しており，成人期の動脈硬化性病変とは必ずしも一致した所見ではないことが報告されている．しかしながら，小児期における内膜肥厚所見に加え，高コレステロール血症，喫煙，高血圧などの他の動脈硬化危険因子が加われば，若年成人で動脈硬化病変へと進展する可能性が考えられる．

文献
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