Transthoracic Doppler Assessment of Coronary Flow Velocity Reserve in Children With Kawasaki Disease

Comparison With Coronary Angiography and Thallium-201 Imaging

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OBJECTIVES

The purpose of this study was to determine the feasibility of coronary flow velocity reserve (CFVR) measurement by transthoracic Doppler echocardiography (TTDE) in children with Kawasaki disease (KD).

BACKGROUND

Doppler-derived CFVR is a reliable marker predicting the presence of myocardial ischemia.

METHODS

We studied 49 patients (median age 11 years) with KD. The CFVR was calculated as the ratio of hyperemic to basal peak (peak CFVR) and mean (mean CFVR) diastolic flow velocities in the posterior descending coronary artery (PD) and left anterior descending coronary artery (LAD). The CFVR measurements by TTDE were compared with the results of coronary angiography, thallium-201 (Tl-201) single-photon emission computed tomography (SPECT), and intracoronary Doppler study.

RESULTS

The CFVR measurements by TTDE were obtained in 92 (94%) of 98 vessels of the PD and LAD in 49 study patients. Both peak and mean CFVRs for 21 stenotic vessels were significantly smaller than those for 35 normal vessels and for 20 vessels with aneurysmal lesions (p < 0.0001). Peak and mean CFVR < 2.0 predicted significant coronary stenosis, as determined by coronary angiography, with sensitivities and specificities of 89% and 96% and 89% and 97%, respectively. Also, both peak and mean CFVRs were correlated with reversible perfusion defects on Tl-201 SPECT (agreement 80%; kappa 0.4). The correlation between peak and mean CFVRs determined by the TTDE and intracoronary Doppler studies in 36 vessels of 23 patients were 0.76 and 0.80, respectively.

CONCLUSIONS

The CFVR measured by TTDE predicts the presence of significant coronary stenosis of either the right coronary artery or LAD, as well as myocardial ischemia of these territories in children with KD.

Early detection and treatment of myocardial ischemia due to coronary lesions in children with Kawasaki disease (KD) would be a clinical advance. Recently, this has become especially important in view of the increasing number of surgical and catheter interventions for severe coronary stenosis in patients with KD (1–3). Noninvasive diagnostic testing, such as perfusion scintigraphy, is used as an accurate tool to detect myocardial ischemia and infarction. However, a significant discordance in the findings between stress perfusion scintigraphy and coronary angiography in children with KD has been reported (4,5). Moreover, perfusion abnormalities correlated poorly with the results of exercise stress echocardiography (6). Coronary flow velocity reserve (CFVR), estimated as the ratio of hyperemic to basal coronary flow velocity, has been assessed invasively (using an intracoronary Doppler flow wire) (7,8) and semi-invasively (by transesophageal Doppler echocardiography) (9,10) in clinical settings. Recently, the value of CFVR, as determined by transthoracic Doppler echocardiography (TTDE), was reported to be useful for the noninvasive assessment of significant coronary stenosis and functional estimates of coronary lesion severity in the left anterior descending coronary artery (LAD) (11–13). To our knowledge, however, these TTDE measurements in the right coronary artery (RCA) have not been established. In addition, the feasibility of TTDE in determining CFVR in children with KD is not known. Thus, the purposes of this study were twofold: 1) to compare the value of CFVR, as determined by TTDE, for the posterior descending coronary artery (PD) and LAD with the results of both coronary angiography and thallium-201 (Tl-201) single-photon emission computed tomography (SPECT) in children with KD; and 2) to compare the CFVR measurement by TTDE with the result of invasive measurement by the Doppler flow wire.

METHODS

Study patients. The study group consisted of 49 patients who were undergoing routine coronary angiography for the evaluation of coronary sequelae in KD. These patients were shown to have had coronary aneurysmal formation in the early stage of the disease, as documented by echocardiography or coronary angiography. All patients had been free of symptoms during their routine daily activities, and none had received beta-adrenergic blocking agents, calcium channel antagonists, or nitrates. Patients with a history of acute myocardial infarction or previous coronary artery bypass graft surgery (CABG) were not included in this study. The
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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CFVR = coronary flow velocity reserve
KD = Kawasaki disease
LAD = left anterior descending coronary artery
PD = posterior descending artery
RCA = right coronary artery
SPECT = single-photon emission computed tomography
TI-201 = thallium-201
TTDE = transthoracic Doppler echocardiography

age range was 3 to 24 years (mean 12, median 11); there were 31 males and 18 females. The interval between the onset of KD and the current study ranged from 2 to 20 years (mean 8, median 6). During this three-year study, of three patients who had severe coronary stenosis with calcification, one underwent rotation and the other two had CABG. Our institutional Committee on Human Research approved the study protocol, and written, informed consent was obtained from the patients or parents of all patients included in the study.

Coronary angiography. Coronary angiography was used as the reference standard for detecting coronary artery stenosis. Localized stenosis was considered significant if there was >50% diameter stenosis in at least one projection. Also, coronary stenosis >75% was defined as moderate to severe stenosis. Calibration of the measurements was accomplished by comparing the patients’ luminal boundary dimensions with those of the catheter used, according to the method of Vieweg et al. (14). Calipers were used in case of questionable findings. Segmental stenosis was defined as a braid-like lesion or several bridging vessels, and its stenotic degree was interpreted by visual analysis. Aneurysms were defined by previously established criteria (15).

Transthoracic Doppler echocardiography. Echocardiography was performed in an outpatient setting and on hospital admission for angiography using the Hewlett-Packard SONOS-5500 with a broad-band transducer (S8 transducer: 3 to 8 MHz; or S12 transducer: 5 to 12 MHz) and the Aloka ProSound SSD-5500 system (Tokyo, Japan) with a 5-MHz transducer.

Recording of PD flow by TTDE. The patients were examined in the left lateral position. The acoustic window was around the apex or slightly right of this position. The approach for the distal part of the RCA first consisted of obtaining an apical four-chamber view. The examination plane was gradually directed rightward and inferiorly until echoes from the tricuspid valve disappeared, and the distal portion was detected as a tubular structure within the posterior atrioventricular groove (16). Next, the transducer was inclined more inferiorly and rotated clockwise to image the PD, which courses toward the apex within the posterior interventricular sulcus. During color Doppler flow mapping, the velocity range was set from ±10 to ±25 cm/s. Then, a careful search for red-coded blood flow was made over the epicardial part of the posterior wall, with simultaneous attempts to optimize the visualization of the PD within the posterior interventricular sulcus (Fig. 1A). Pulsed-wave Doppler recording was attempted with the sample volume positioned on the color signal in the PD. All studies were continuously recorded on 0.5-in. super-VHS videotape for off-line analysis.

Recording of LAD flow by TTDE. Transthoracic Doppler echocardiography was performed to image the LAD in a cross section, as previously described (11,12,16). In brief, after imaging the long-axis view of the left ventricle from the left parasternal border or around the mid-clavicular line in intercostal space 3, 4, or 5, the examination plane was gradually directed leftward and laterally to visualize the mid or distal portion of the LAD under color flow mapping guidance (Fig. 1B). The flow velocity curve was recorded using a pulsed Doppler technique, as described in recording of PD flow.

Study protocol for CFVR. Doppler recordings of coronary flow velocity in both the PD and LAD were obtained at rest and after dipyridamole administration (0.56 mg/kg body weight intravenously [IV] for 4 min) (12,17). The angle between color flow and the Doppler beam was maintained as much as possible during hyperemic testing. In patients who did not show an increase >15% in heart rate or ST–T–segment changes on the electrocardiogram (ECG) 8 min after the start of dipyridamole infusion, additional dipyridamole (0.25 mg/kg IV for 2 min) was administered, because the standard dose may not produce consistently maximal vasodilation (17). All patients underwent continuous heart rate and ECG monitoring. Blood pressure was recorded at baseline, every minute for 10 min after beginning dipyridamole infusion, and after recovery. In the present study, successful detection of coronary flow was defined as optimal contour definition of at least the diastolic curve in the PD and LAD. Peak and mean diastolic velocities were measured by tracing the contour of the spectral Doppler signal using the computer incorporated in the ultrasound unit. An average of the measurements was obtained from three cardiac cycles. The CFVR was calculated as the ratio of hyperemic to basal peak (peak CFVR) and mean (mean CFVR) diastolic flow velocities.

Dipyridamole stress TI-201 SPECT. Thallium-201 SPECT was performed within three months of the CFVR studies by TTDE. Single-photon emission computed tomography was performed using a single-head gamma scintillation camera equipped with a low-energy, all-purpose, parallel-hole collimator. Dipyridamole was used as a hyperemic agent, as described previously (17). The initial images were recorded 5 min after the injection of thallium, and the delayed images 3 to 4 h later. On the SPECT images, defects in the anterior wall and septal region were allocated to the LAD, and inferior defects to the RCA. Apical defects extending to the inferior wall were considered to be located in the RCA region. Perfusion in each segment on the stress and redistribution studies was scored on a scale of 0 (no
uptake) to 3 (normal). A defect with improvement of >1 grade was called reversible, and other defects were deemed persistent.

**Intracoronary Doppler flow wire studies.** In 23 patients included in the latter part of this study, a 0.014-in. (0.36-mm), 15-MHz Doppler flow wire (EndoSonics, Inc., Rancho Cordova, California) was advanced through a 4F guiding catheter, and its position was adjusted to obtain a maximal and intense spectral flow velocity signal in the distal portion of the RCA and LAD. Intravascular velocity measurement in these sites was made at rest and after IV administration of 0.14 mg/kg per minute of adenosine triphosphate for 4 to 6 min (18), while monitoring heart rate and blood pressure.

**Statistical analysis.** Continuous data are expressed as the mean value ± SD. Differences between two different parametric variables at rest and during hyperemia were tested using the paired, two-tailed Student t test. Analysis of variance and subsequently the post-hoc Scheffé F test were performed to compare coronary flow velocity param-
eters among the three groups, using Statview version 4.5 (Cary, North Carolina). The chi-square test (1 × m contingency table) was used to analyze the incidence of perfusion defects on SPECT. A p value <0.05 was considered significant. Correlation between CFVRs measured by the Doppler and invasive methods was evaluated using both linear regression analysis and the Bland-Altman method to assess the limits of agreement between repeated measurements (19). The cut-off value of CFVR was determined as the highest sum of sensitivity and specificity, as compared with the results of coronary angiography, using receiver-operator curve analysis. Agreement between Doppler and nuclear data was assessed by the kappa statistic (20). Interobserver variability was assessed for the aforementioned flow velocity parameters in 10 recordings from 10 patients and was calculated as the standard deviation of the differences between the first and second determinations (2- to 4-month interval) and expressed as a percentage of the average.

RESULTS

Coronary angiography. Forty-nine patients were classified into three groups on the basis of each of the LAD and RCA status on the coronary angiograms, as there were no stenotic lesions in the left main and circumflex coronary arteries. Group 1 consisted of 18 patients with no evidence of significant coronary lesions. Group 2 consisted of 16 patients with coronary aneurysms in 20 vessels, 10 of which were in the LAD and 10 in the RCA. Of these patients, giant (>8 mm) or multiple aneurysms, or both, were seen in the RCA (n = 5) and LAD (n = 4). Group 3 consisted of 15 patients with stenotic lesions in 23 vessels (RCA: n = 11; LAD: n = 12). Among these, eight patients had coronary stenosis of the RCA and LAD. The obstructive lesions included 13 localized stenoses with or without aneurysms, 4 segmental stenoses, and 4 occlusions associated with collateral vessels. Their stenotic degree was judged as 50% to 75% narrowing in 10 vessels and >75% narrowing in 13 vessels.

Transesophageal Doppler echocardiography. The imaging and recording time of the echocardiographic studies, including the dipyridamole stress test, was from 20 to 45 min/patient. Doppler diastolic flow velocity curves suitable for analysis of LAD and PD flow were obtained in 92 vessels (PD: n = 46; LAD: n = 46) in 49 patients. We could not obtain a Doppler recording in two of four vessels with occlusion, but in the other two vessels, diastolic retrograde or mixing of diastolic anterograde and retrograde flow through the collateral arteries was clearly detected in both the PD and distal LAD. Therefore, these 92 vessels of the PD and LAD comprised the study groups in which we compared TTDE data with angiographic and TI-201 SPECT results.

Doppler and hemodynamic characteristics. The baseline heart rate was lower in group 3 compared with groups 1 and 2 (p < 0.05), but systolic and diastolic blood pressure did not differ among the three groups (Table 1). The heart rate increased by ~20% (p < 0.01), and systolic and diastolic blood pressure decreased during infusion (p < 0.05), although there was no significant difference in these variables among the three groups (Table 1). No major adverse reactions occurred after dipyridamole infusion, and only one patient with nausea and palpitation received theophylline infusion. No patients showed ST-segment depression on the ECG.

Transesophageal CFVR versus coronary angiography. Both peak and mean CFVRs in group 3 were significantly smaller than those in groups 1 and 2 (p < 0.0001) (Table 2). Also, the CFVR values were significantly lower in group 2 than in group 1 (p < 0.05 for peak CFVR; p < 0.01 for mean CFVR). Figures 2 and 4 depict a clear difference in the spectral Doppler flow profile during hyperemia in the

Table 1. Hemodynamic Data at Rest and During Hyperemia in the Three Groups of Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Heart Rate (beats/min)</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Hyperemia</td>
<td>Baseline</td>
</tr>
<tr>
<td>Group 1</td>
<td>18</td>
<td>11, 10</td>
<td>84 ± 15</td>
</tr>
<tr>
<td>Group 2</td>
<td>16</td>
<td>14, 11</td>
<td>82 ± 18</td>
</tr>
<tr>
<td>Group 3</td>
<td>15</td>
<td>15, 14</td>
<td>73 ± 94‡</td>
</tr>
</tbody>
</table>

*p < 0.01 and †p < 0.05 when comparing hyperemia versus baseline. ‡p < 0.05 vs. group 1 and ‡p < 0.05 vs. group 2 among the three groups. Data are presented as the mean value ± SD, except for age.

BP = blood pressure.

Table 2. Comparison Between Coronary Artery Lesions Demonstrated by the Angiography and CFVR Values Measured by Transthoracic Doppler Echocardiography

<table>
<thead>
<tr>
<th>Group</th>
<th>NL (n = 35)</th>
<th>AN (n = 20)</th>
<th>NL (n = 10)</th>
<th>ST (n = 21)</th>
<th>NL (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CFVR</td>
<td>3.4 ± 0.8</td>
<td>2.8 ± 0.6*</td>
<td>3.5 ± 0.8</td>
<td>1.6 ± 0.4§</td>
<td>3.5 ± 0.9</td>
</tr>
<tr>
<td>Mean CFVR</td>
<td>3.2 ± 0.6</td>
<td>2.7 ± 0.5†</td>
<td>3.4 ± 0.8</td>
<td>1.5 ± 0.3‡§</td>
<td>3.3 ± 0.7</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01 vs. group 1; §p < 0.0001 vs. group 1; ‡p < 0.0001 vs. group 2. Data are presented as the mean value ± SD.

AN = vessels with aneurysm; CFVR = coronary flow velocity reserve; NL = normal vessel; ST = vessels with stenosis.
Figure 2. (Upper left panel) Selective right coronary angiogram demonstrating multiple aneurysms in a 16-year-old patient. (Upper middle and right panels) Intracoronary Doppler flow wire tracings in the posterior descending artery (PD) at rest (middle) and after adenosine triphosphate infusion (right). (Lower panels) In the same patients, transthoracic Doppler flow tracing are shown in the PD at rest and after dipyridamole infusion.
patients from groups 2 and 3. When CFVR $<2.0$ was used as the cut-off point, the sensitivity and specificity for the presence of significant coronary stenosis were 89% and 96% for peak CFVR and 89% and 97% for mean CFVR, respectively. Moreover, CFVR values in patients with $>75\%$ stenosis were significantly lower than those in patients with 50% to 75% stenosis (peak CFVR: $1.8 \pm 0.3$ vs. $1.4 \pm 0.3$; mean CFVR: $1.7 \pm 0.4$ vs. $1.4 \pm 0.3$; $p < 0.05$).

Each of the two patients with false-negative results in group 3 had 50% to 75% stenosis of the LAD or well-developed recanalization in the middle RCA. Of three false-positive patients in group 2, two had a single aneurysm and another had multiple coronary aneurysms.

Thallium-201 SPECT versus angiography and transthoracic CFVR. The reversible and persistent perfusion defects in the LAD and RCA territories on Tl-201 SPECT in 49 study patients are summarized in Table 3. The incidence of reversible defects was significantly higher in the stenotic vessel territories of group 3 than in those of groups 1 and 2 ($p < 0.01$), but persistent defects showed a similar incidence among the three groups of patients. The sensitivity of SPECT imaging for showing a reversible defect to detect significant stenosis $>50\%$, as determined by angiography, was 60%, with 89% specificity. When a reversible perfusion defect was interpreted as myocardial ischemia, the percent agreement between both peak and mean CFVR $<2.0$ and the reversible perfusion defect on SPECT imaging was 80% (kappa 0.4).

Transthoracic versus intracoronary CFVR. Included in this study were 36 vessels of 23 patients in whom we could record optimal coronary flow. The heart rate at baseline and during hyperemia was not different between the intracoronary and transthoracic Doppler methods (baseline: $88 \pm 20$ vs. $82 \pm 20$ beats/min; hyperemia: $108 \pm 20$ vs. $103 \pm 21$ beats/min). Also, systolic and diastolic blood pressures did not differ between the studies. Correlations between peak and mean CFVRs, determined by transthoracic and intracoronary Doppler methods, were 0.76 and 0.80, respectively, and the mean differences between these two methods were $0.32 \pm 0.48$ and $0.20 \pm 0.41$ (Fig. 3).

Changes in CFVR in patients undergoing rotablation or CABG. Peak and mean CFVR in five stenotic vessels in three patients who had successful rotablation ($n = 1$) or CABG ($n = 2$) increased from $1.3 \pm 0.2$ to $2.2 \pm 0.3$ and $1.2 \pm 0.1$ to $2.1 \pm 0.3$ ($p < 0.01$), respectively. Figure 4 depicts a typical patient showing an increase in CFVR after the procedure. These TTDE results in three patients were confirmed by the intracoronary Doppler flow wire technique (Fig. 5), angiography, or both.

Observer variability. Interobserver and intraobserver variabilities for CFVR measurements were 6.4% and 4.2% for the PD and 5.9% and 4.0% for the LAD, respectively.

DISCUSSION

Measurement of CFVR by TTDE. We believe that this is the first clinical study to measure CFVR in the distal RCA by TTDE. Blood flow profiles in the PD and LAD were predominantly diastolic, which concurs with previous invasive studies (8,21,22). We could measure CFVR using diastolic velocities obtained in the PD and LAD with a high rate of success. Moreover, the present study showed a good...
correlation between both peak and mean CFVR determined by TTDE and those determined by an invasive method. This indicates that TTDE is an adequate tool for determining CFVR in children.

**CFVR measured by TTDE versus coronary angiography.** Our study demonstrated that CFVR enabled separation of the two patient groups (those with and without significant coronary stenosis), as determined by coronary angiography, and this situation was not affected by the presence or absence of contralateral coronary artery lesions (stenoses or aneurysms). Moreover, CFVR values in patients with $>75\%$ stenosis were significantly lower than those in patients with $50\%$ to $75\%$ stenosis. This indicates that CFVR enables the detection of specific epicardial stenosis in the LAD and RCA, in agreement with previous reports (11,12). Previous studies have shown controversial results of the effects of aneurysms on CFVR (23,24). The CFVR value was significantly lower in the patient group with coronary aneurysms than in the patient group with normal coronary arteries. However, it should be stressed

**Table 3.** Relationship Between Coronary Artery Lesions and Perfusion Defects on Thallium-201 Single Photon Emission Computed Tomography

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NL (n = 36)</td>
<td>AN (n = 20)</td>
<td>NL (n = 12)</td>
</tr>
<tr>
<td>Reversible defect</td>
<td>3 (8%)</td>
<td>3 (15%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Persistent defect</td>
<td>5 (14%)</td>
<td>3 (15%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (22%)</td>
<td>6 (30%)</td>
<td>4 (33%)</td>
</tr>
</tbody>
</table>

<sup>†</sup>p < 0.01 vs. group 1. <sup>‡</sup>p < 0.01 vs. group 2. Data are presented as the number (%) of patients.

Abbreviations as in Table 2.
that 85% of vessels associated with coronary aneurysms, even in large or multiple aneurysms, did not show reduced CFVR <2.0.

CFVR measured by TTDE versus TI-201 SPECT. Recently, Daimon et al. (13) reported that CFVR measured by TTDE may provide data equivalent to those obtained by TI-201 SPECT for physiologic estimation of the severity of LAD stenosis. Our results in children who had KD showed that low CFVR values, coupled with reversible perfusion defects on 201-TI SPECT, but discordant results, were obtained in 20% of the study patients. Previous investigators reported that in young children, there are age-related changes in the normal radionuclide distribution pattern for myocardial scintigraphy (17,25). Furthermore, it is known that perfusion scintigraphy has a limited capability, particularly in multivessel coronary disease (26,27). This may explain the relatively low agreement found in the current study. In this regard, we can consider the effect of coronary microcirculation after KD on scintigraphic imaging, because some pathologic studies have demonstrated interstitial fibrosis of the myocardium and intramural small coronary artery lesions in some patients in the late stage of KD (28,29). It was interesting that all five patients with normal epicardial coronary arteries associated with reversible or persistent perfusion defects showed CFVR values >2.0. Further studies are needed to explain the clinical significance of abnormal scintigrams in patients without epicardial coronary stenosis after KD.

Study limitations. Our study has some limitations. First, our transthoracic Doppler method could not detect coronary flow in six vessels (3 LAD and 3 PD). Technical improvements and recently developed contrast-enhanced Doppler echocardiography may reduce this problem by increasing the amplitude of the coronary flow signal (12). Second, the number of study subjects was small. In future investigations, more patients should be studied using the present method. Third, the PD is a terminal extension of the RCA, but in a minority of patients, it branches from the left circumflex artery. Fourth, interobserver variability was assessed on the basis of prerecorded data. Finally, transthoracic and intracoronary Doppler evaluations were not performed simulta-
neously, and dipyridamole was used during the former evaluation instead of adenosine triphosphate that was used during the latter evaluation. Also, intracoronary Doppler evaluation was made through a guiding catheter inserted during the latter evaluation. Also, intracoronary Doppler evaluation instead of adenosine triphosphate that was used neously, and dipyridamole was used during the former evaluation. In children with angiographically normal coronary arteries, Circulation 1995;92:2457–62.


