Coronary Flow Velocity and Coronary Flow Velocity Reserve in Children with Ventricular Septal Defect

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To assess coronary flow characteristics in congenital heart defect with left ventricular (LV) volume overload, we examined 24 children (mean 12.1±7.1 months) with ventricular septal defect. The pulmonary to systemic flow ratio ranged from 1.1 to 3.0. Control group consisted of 10 age-matched children who had a history of Kawasaki disease with angiographically normal coronary artery in the acute phase. LV end-diastolic volume and LV mass were measured by left ventriculogram. With Doppler flow guide wire (0.014-inch), average peak flow velocity (APV) in left anterior descending coronary artery was recorded at rest and during hyperemia (0.16 mg/kg/min adenosine infusion intravenously). Coronary flow velocity reserve (CFVR) was calculated as the ratio of hyperemic/baseline APV. Seven patients were also studied 5-7 months after surgery. Compared with control subjects, CFVR was significantly reduced in patients with LV volume overload (1.78±0.24 vs. 2.66±0.42, p<0.0001) because baseline APV was significantly greater (30±8 vs. 23±5 cm/sec, p=0.0027). Significant correlations were observed between CFVR and Qp/Qs, baseline APV, LV end-diastolic volume, or LV mass. Stepwise regression analysis showed that baseline APV and Qp/Qs were important determinants of CFVR (CFVR=2.64−0.202 [Qp/Qs]−0.015 [APV] r=0.83, p<0.0001). In 7 patients with LV volume overload, CFVR improved significantly after surgery because of reduction of baseline APV. CFVR is limited in patients with LV volume overload because of the elevation of baseline resting APV. LAD flow pattern is dependent on LV volume overload level and its changes after surgery.

ventricular septal defect; coronary flow velocity reserve

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Coronary flow velocity and coronary flow velocity reserve (CFVR) measurements have provided useful clinical and physiologic information in pediatric patients with congenital or acquired heart disease (Doty et al. 1984; Hamaoka et al. 1992, 1998; Hijazi et al. 1994; Bengel et al. 1998; Donnelly et al. 1998; Pitkanen et al. 1998; Yates et al. 2000; Hauser et al. 2001; Singth et al. 2001; Oskarson et al. 2002; Yasuoka et al. 2002; Aoki et al. 2003). Recently, Doppler-tipped angioplastic 0.018- or 0.014-inch Doppler guide wire has been developed to measure coronary blood flow velocity even in children. Although the Doppler guide wire is used in pediatric patients with coronary sequelae of Kawasaki disease, myocardial disorder, and other anatomic cardiac anomalies, there is limited information on coronary flow velocity and CFVR in pediatric patients with left ventricular (LV) volume overload caused by ventricular septal defect (VSD). Using Doppler echocardiographic technique, an increase in left anterior descending coronary artery (LAD) flow velocity has been demonstrated in VSD patients with LV volume overload caused by a left-to-right shunt (Harada et al. 2001, 2002; Yasuoka et al. 2002). Because an increase in resting coronary flow has been reported to be a main mechanism of restriction of coronary flow reserve in adults patients with aortic regurgitation or mitral regurgitation (Pichard et al. 1983; Nitenberg et al. 1988; Akasaka et al. 1998), reduced CFVR would be also expected in VSD patients with LV volume overload. Therefore, to assess the physiological characteristics of coronary flow-velocity dynamics in children with LV volume overload, we examined phasic coronary flow-velocity patterns at rest and during hyperemic responses with a Doppler guide wire in children with VSD.

**METHODS**

**Study subjects**

Twenty four patients (mean 12.1±7.1 months) with isolated VSD who underwent heart catheterization were prospectively enrolled in the study. Of these cases, heart catheterization and coronary flow measurements were performed before and at 5-7 months after surgery in 7 patients. The control group consisted of 10 age-matched children who had a history of Kawasaki disease with normal coronary angiographic findings. No patient had a history of ischemic attack or chest pain. The duration from the onset of Kawasaki disease to study onset ranged from 0.6 to 2 years. No subjects received drug therapy. The nature of the study was discussed with each patient’s parents, and informed consent for the research protocol was obtained before cardiac catheterization.

**Cardiac catheterization and angiographic studies**

Cardiac catheterization was performed by the femoral approach after local anesthesia. Sedation with thiopental sodium (3 mg/kg) was intravenously administered when necessary. Left and right heart pressure data were recorded using a fluid-filled catheter-transducer system before left ventricular angiogram. The pulmonary to systemic flow ratio (Qp/Qs) was measured by the Fick’s method. LV mass and volumes were measured from bi-plane cineventriculograms in the right anterior and axial left anterior oblique projections at 50 frames/sec, and cavity borders were traced manually at end-diastole and end-systole during sinus rhythm. LV end-diastolic and end-systolic volumes were calculated by simpson’s rule and indexed for body surface area as the end-diastolic volume index and end-systolic volume index, respectively. Ventricular mass was calculated as previously described by Rackley et al. (1964) and indexed for body surface area, expressed as g/m².

**Doppler guide wire examinations**

After routine cardiac catheterization and left ventriculography, phasic coronary flow velocity patterns were recorded with a 175-cm-long, 0.014-inch flexible steerable angioplastic guide wire with a 15-MHz piezoelectric ultrasound transducer integrated into the tip and a velocimeter (Jometrix FloWire FloMap system, Jomed Inc.,
Cordova, CA, USA). Pulse repetition frequency of the Doppler flowmeter was variable from 12 to 96 kHz within the velocity range selected. The forward directed ultrasound beam diverges in a 28 degree arc from the long axis. The tip of the Doppler guide wire was advanced through a 4F guiding Judkins catheter into the proximal portion of LAD. An optimal Doppler signal was obtained by moving the guide wire slightly within the vessel lumen and adjusting the range gate control. In our study, coronary flow measurements were performed with the guiding catheter withdrawn from the ostium of LAD. The guiding catheter obstruction that interfered with coronary flow was minimized in all cases by 4F guiding catheters. No patients had complications related to cannulation or a guidewire. During the Doppler study, a 12-lead surface electrocardiogram and pressure wave form at the tip of the guiding catheter in the ascending aorta were monitored continuously. All studies were recorded on 0.5-in. s-VHS videotape for off-line analysis.

**CFVR Measurement**

After baseline recordings, adenosine triphosphate (ATP) was infused in the right antecubital vein at a dose of 160 μg per body weight/min. The time average of the instantaneous spectral peak velocity (average peak flow velocity [APV]) was measured from the phasic coronary flow velocity recordings. The ratio of hyperemic APV to baseline APV was calculated as an index of CFVR.

**Statistics**

Values are expressed as the mean±s.d. The two groups were compared using two-tailed unpaired Student’s t-test. For cases involving VSD patch closure, a paired two-tailed t-test was performed to compare the data between before and after surgery. The relations between coronary flow data and other hemodynamic parameters were assessed by linear regression analysis. Stepwise regression analysis was also performed to estimate the most important determinant of coronary flow velocity reserve among hemodynamic parameters. A p-value of <0.05 was considered statistically significant.

**RESULTS**

**Clinical characteristics and hemodynamic data at rest**

As indicated in Table 1, heart rate in VSD patients was higher than in controls (123±18 vs. 107±19 beats/min, p=0.025). There were no significant differences in systolic blood pressure and rate-pressure product between the two groups. LV end-diastolic volume index and LV mass index were significantly greater in VSD patients than those in control subjects. APV were significantly higher in VSD patients than in control subjects. APV increased significantly with heart rate, Qp/Qs, LV end-diastolic volume, and LV mass (r=0.58, p=0.024, 0.63, p=0.0007, r=0.55, p=0.00045, r=0.60, p=0.0014, respectively). There was no significant relationship between APV and rate-pressure product.

**Coronary flow velocity data during ATP infusion**

Table 2 shows coronary flow data during ATP infusion. ATP infusion increased heart rate in the two groups (123±18 vs. 132±20 beats/min in patients and 107±19 vs. 122±18 beats/min in controls, p<0.0001, respectively). Systolic blood pressures in the two groups decreased significantly during ATP infusion (92±11 vs. 78±3 mmHg in patients and 98±9 vs. 86±14 mmHg in controls, p<0.0001, respectively). APV in the two groups increased significantly during hyperemia (30±8 vs. 54±10 cm/sec in patients and 23±5 vs. 59±14 cm/sec, p<0.0001, respectively). CFVR in VSD patients was significantly lower than that in controls (1.78±0.24 vs. 2.66±0.42, p<0.0001). Figs. 1 and 2 show examples of LAD flow velocity recordings at rest and during hyperemia in a VSD patient (Fig. 1) and a normal control (Fig. 2).
Table 1. Hemodynamic data and echocardiographic measurements

<table>
<thead>
<tr>
<th>Age(months)</th>
<th>VSD (n=24)</th>
<th>Control (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.1±7.1</td>
<td>13.2±9.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Hemodynamic data**

- Heart rate (beats/min.) 123±18 vs. 107±19, p=0.025
- Systolic blood pressure (mmHg) 92±11 vs. 98±9, NS
- Rate-pressure product (mmHg/min.) 11118±1795 vs. 10473±2695, NS
- Qp/Qs 1.9±0.5 vs. 2.0±0.5
- LVEDV (ml/BSA) 89±20 vs. 65±12, p=0.0016
- LVM (gm/BSA) 86±15 vs. 56±10, <0.0001
- LVEF 60±4 vs. 63±5, NS

**LAD measurements**

- Average peak flow velocity (cm/sec.) 30±8 vs. 23±5, 0.0027

Qp/Qs, pulmonary to systemic flow ratio; LVEDV, end-diastolic volume; LVM, mass; LVEF, ejection fraction; LAD, left anterior descending coronary artery; BSA, body surface area; NS, not significant.

Table 2. Hemodynamic data and echocardiographic measurements during adenosine infusion

<table>
<thead>
<tr>
<th></th>
<th>VSD (n=24)</th>
<th>Normal (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>123±18</td>
<td>107±19</td>
</tr>
<tr>
<td>Adenosine</td>
<td>132±20</td>
<td>122±18</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>92±11</td>
<td>78±3</td>
</tr>
<tr>
<td>Average peak flow velocity (cm/sec.)</td>
<td>30±8</td>
<td>54±10</td>
</tr>
<tr>
<td>Coronary flow velocity reserve</td>
<td>1.78±0.24</td>
<td>2.66±0.42</td>
</tr>
</tbody>
</table>

*p<0.0001 vs. Rest, ^p<0.0001 vs. Normal.

Fig. 1. An example of coronary flow velocity recordings in the left anterior descending coronary artery at rest and during hyperemia in a patient with ventricular septal defect.
Fig. 2. An example of coronary flow velocity recordings in the left anterior descending coronary artery at rest and during hyperemia in a control subject.

![Coronary Flow Velocity Recordings](image)

**Rest**

**ATP**

Fig. 3. Relationships between CFVR and baseline APV, Qp/Qs, LV end-diastolic volume, and LV mass. CFVR vs. APV, $y=2.60-0.026x$, $r=-0.78$, $p<0.0001$; CFVR vs. Qp/Qs, $y=2.51-0.38x$, $r=-0.72$, $p<0.0001$; CFVR vs. LVEDV index, $y=2.46-0.0077x$, $r=-0.64$, $p=0.0005$; CFVR vs. LV mass index, $y=2.72-0.011x$, $r=-0.70$, $p<0.0001$. 
Coronary Flow Reserve

Relationships between CFVR and hemodynamic parameters in VSD patients

As indicated in Fig. 3, significant correlations were observed between CFVR and baseline APV, Qp/Qs, LV end-diastolic volume, or LV mass ($r=-0.78$, $p<0.0001$, $r=-0.72$, $p<0.0001$, $r=-0.64$, $p=0.0005$, and $r=-0.70$, $p<0.0001$, respectively). There was no significant relationship between CFVR and rate-pressure product. Stepwise regression analysis showed that resting APV and Qp/Qs were important determinants of CFVR ($\text{CFVR}=2.64 -0.202 \text{[Qp/Qs]} -0.015 \text{[APV]}$, $r=0.83$, $p<0.0001$).

Coronary flow data before and after surgery

Table 3 shows hemodynamic data and echocardiographic measurements before and after surgery. There were no significant differences between before and after surgery in systolic blood pressure and rate-pressure product, although heart rate, LVEDV-diastolic volume, and LV mass were significantly greater before surgery compared with those after surgery ($131\pm11$ vs. $122\pm9$ beats/min, $p=0.02$, 103±23 vs. 71±10 ml/body surface area, $p=0.0067$, and 96±12 vs. 70±5 gm/body surface area, $p=0.001$). Baseline APV was significantly higher before surgery compared with that after surgery ($33\pm10$ vs. $22\pm5$ cm/sec, $p=0.0026$), although there was no significant differences in maximal hyperemic APV before and after surgery. As a result, CFVR before surgery was significantly smaller than that after surgery ($1.63\pm0.14$ vs. $2.43\pm0.42$, $p=0.0015$).

DISCUSSION

In the present study, using Doppler flow guide wire method, we demonstrated the coronary flow characteristics in children with LV volume overload induced by a left-to-right shunt though a VSD.

In the present study, the APV in the patients with VSD was significantly higher than in controls. The mechanism is unclear. Myocardial blood flow at rest depends on oxygen demand, which in turn is related to cardiac work. The product of heart rate and peak systolic pressure, the so-called
rate-pressure product, has been shown to correlate with measured left ventricular myocardial oxygen consumption (Shaddy et al. 1989). However, the rate-pressure products did not differ between the two groups in this study. Increases in coronary flow have been shown to be also related to the conditions that result in increases in LV preload, LV mass, and volume overload (Shaddy et al. 1989; McGinn et al. 1990). All these conditions are probable in patients with VSD, and thus LAD flow could be influenced by each of these factors to some degree. Consequently, a considerable scatter was observed in correlations between LAD flow velocity and increases in Qp/Qs, LV end-diastolic volume, or LV mass. Because an increased Qp/Qs is the common determinant of LV dilatation and increased LV mass (Jarmakani et al. 1969), the best correlation found between Qp/Qs and LAD APV may be reasonable.

In the present study, CFVR was limited in the patients with VSD because of increase in resting coronary flow velocity without any change in maximal hyperemic blood flow velocity. Coronary flow reserve has been reported to be restricted in patients with increased LV mass secondary to volume overload caused by mitral regurgitation or aortic regurgitation (Pichard et al. 1983; Nitenberg et al. 1988; Akasaka et al. 1998). An increase in resting coronary flow has been demonstrated to be the primary mechanism of restriction of coronary flow reserve (Pichard et al. 1983; Nitenberg et al. 1988; Akasaka et al. 1998), which is consistent with our findings. Furthermore, this restriction of CFVR in the patients with VSD improved after successful surgery because of reduction in resting coronary flow velocity. Thus, increase in resting coronary flow velocity induced by increase in Qp/Qs, LV end-diastolic volume, and LV mass due to a left-to-right shunt may be main mechanisms of restricted CFVR in patients with VSD. The findings obtained in the present study suggest that the coronary circulation can adapt to the increased myocardial oxygen demand under LV volume overload, but is unable to modify its capacity for maximal coronary flow, so that the increase in resting flow is obtained at the expense of coronary reserve.

As we revealed, increase in resting coronary flow is a main mechanism of restriction of CFVR. Reduced CFVR has been proposed to be a mechanism of the progressive deterioration of LV function (Starling et al. 1993). Although we had no patients with LV dysfunction despite reduced CFVR, further increase in coronary flow velocity and, consequently, further reduction in CFVR induced by increased metabolic demand such as tachycardia with fever during respiratory infection would result in LV dysfunction. Given the increased myocardial oxygen demand under these conditions, a reduction in heart rate may decrease LAD flow velocity and increase CFVR. Thus, from the point of view of coronary flow circulation, vasodilators (decrease in Qp/Qs) or/and digoxin (decrease in heart rate) might have the advantage of reducing resting coronary flow velocity and improving CFVR in patients with VSD. Further study is required to clarify this issue.

Study limitations

Although the Doppler guide wire provides a convenient method of obtaining phasic flow-velocity data in coronary arteries, the limitations of intracoronary Doppler catheter techniques have been described in detail (Marcus et al. 1987). Flow-velocity measurements do not provide an absolute value but are linearly related to changes in absolute flow when vessel area remains unchanged. It is possible that the results seen in the present study may relate to changes in the lumen area of the coronary artery during hyperemia. We cannot exclude the possibility that dilation of the proximal LAD may have led to augmented flow with less of an increase in velocity in the patients with VSD. In this study, control subjects examined in the present study were not entirely normal. Our patients had no coronary lesions at acute stage of Kawasaki disease. Although Iemura et al. (2000) showed that patients with Kawasaki disease who had normal coronary arteries in the acute phase have normal coronary wall morphol-
ogy and vascular function, we have no data regarding this.

Conclusions
CFVR is limited in patients with VSD because of the elevation of baseline resting APV. LAD flow pattern is dependent on LV volume overload level and its changes after surgery.

References


Pichard, A.D., Smith, H., Holt, J., Meller, J. & Gorlin,


