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Effects of Dobutamine on Coronary Flow Velocity Response and Their Relations to Age

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YASUOKA, K., HARADA, K., TAMURA, M., TOYONO, M., AOKI, M. and TAKADA, G. *Effects of Dobutamine on Coronary Flow Velocity Response and Their Relations to Age*. Tohoku J. Exp. Med., 2001, **195** (3), 171-179 —— The purpose of this study was to assess the effects of low-dose dobutamine on left ventricular (LV) functional and coronary flow reserves using transthracic echocardiography. The study group consisted of 30 children aged from 5 months to 16 years (mean 4.8±4.4 years). Echocardiographic studies were repeated before and during dobutamine infusion (5 μg/kg per minute). The peak diastolic velocity in the left descending coronary artery (LAD) was recorded by pulsed-Doppler under the guidance of color Doppler flow mapping. The coronary flow velocity (CFV) response was calculated as the ratio of LAD peak flow velocity at dobutamine infusion to basal LAD peak flow velocity. Left ventricular contractility was calculated by two-dimensionally directed M-mode echocardiography. The rate-corrected mean velocity of circumferential fiber shortening (mVcfc) and LV end-systolic wall stress (ESS) were used as indices of contractility. Adequate spectral Doppler recordings of the LAD peak flow velocity for the assessment of CFV response were obtained in 26 of 30 patients (87%). The LAD peak flow velocity at dobutamine infusion increased significantly compared with the basal values. The CFV response in the younger children was low and increased significantly with age. The CFV response did not show significant correlations with the changes in heart rate, systolic blood pressure, rate-pressure product, nor ESS during dobutamine infusion. However, a significant relationship between the CFV response and the percent change of mVcfc was observed. In the present study using high frequency transthoracic echocardiography, we demonstrated the age-related changes in CFV response and LV functional reserve by dobutamine infusion. Responses of LV contractility and coronary flow to dobutamine are less sensitive in youngerchildren and increased with increasing age. ——
dobutamine; coronary flow; transthoracic doppler echocardiography
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Dobutamine is a relatively short-acting $\beta 1$ agonist with primarily inotropic action at low doses and it is an ideal drug for studying cardioselective responses to catecholamines (Berg et al. 1993; De Wolf et al. 1995, 1998a, b; Harada et al. 1996). Some reports from animal and human studies show an age-related changes in cardiovascular response to dobutamine (Gauthier et al. 1975; Driscoll et al. 1979; Perkin et al. 1982; Martinez et al. 1992). For example, the neonatal cardiovascular system has been reported to be less sensitive to dobutamine (Perkin et al. 1982; Martinez et al. 1992). Since contractile reserve is dependent on the level of myocardial blood flow at rest and during inotropic stimulation (Lee et al. 1997; Harada et al. 2001), the magnitude of the coronary flow response to dobutamine, called the coronary flow reserve, would be expected to be less sensitive in infants. However, there is limited information about age-related changes in the effects of dobutamine on coronary blood flow. This lack of data may be related with the difficulty in adopting invasive procedures in children for research purpose.

Recently, several studies have reported that the flow velocity in the left anterior descending coronary artery (LAD) can be measured using transthoracic two-dimensional and Doppler echocardiography in children (Jureidini et al. 1998, 2000; Harada et al. 1999). Noninvasive measurement of coronary flow velocity (CFV) using transthoracic echocardiography has been shown to reflect invasive measurement of coronary flow velocity CFV by Doppler guide wire method (Hozumi et al. 1998). Therefore, in the present study, we applied this technique to assess the influence of dobutamine on CFV and its relations to age and left ventricular (LV) function in children.

METHODS

Subjects

The study group consisted of 30 patients aged 5 months to 16 years (4.8 ± 4.4 years) without valvular heart disease or arrhythmia. All of the patients had a history of Kawasaki disease without stenosis or aneurysm formation of coronary artery. Myocardial scincigraphy showed no significant ischemic lesion in each subject. No subjects received drug therapy. Low-dose dobutamine used in this study was presumed to be harmless for the subjects. All parents received an explanation of the study and gave their informed consents.

Study protocol

Echocardiography was performed in the cardiac catheterization laboratory after routine right and left heart catheterization. Premedication with pethidine hydrochloride was administered subcutaneously 1 hour before catheterization. Studies were performed in a quiet and resting state. Sedation with thiopental sodium (3 mg/kg) was used intravenously when necessary. After baseline recordings were obtained, continuous dobutamine infusion was initiated at 5 μg/kg per minute. To attain a steady-state dobutamine concentration, dobutamine was infused for 15 minutes, and echocardiographic recordings were repeated (Fig. 1).

M-mode Echocardiography

Two-dimensional echocardiogram and M-mode recording of the left ventricular minor axis were obtained with an Aloka SSD 5500 ultrasonoscope with a 3.5 or 5.0 MHz transducer. Simultaneous recordings of LV M-mode echocardiography, a phonocardiogram, right or left femoral arterial pressure, and electrocardiogram were obtained. The M-mode measurements were performed according to the recommendations of American Society of Echocardiography (Sahn et al. 1978).

LV shortening fraction was calculated as (end-diastolic dimension-end-systolic dimension)/end-diastolic dimension. The ejection time measured from the simultaneous carotid or

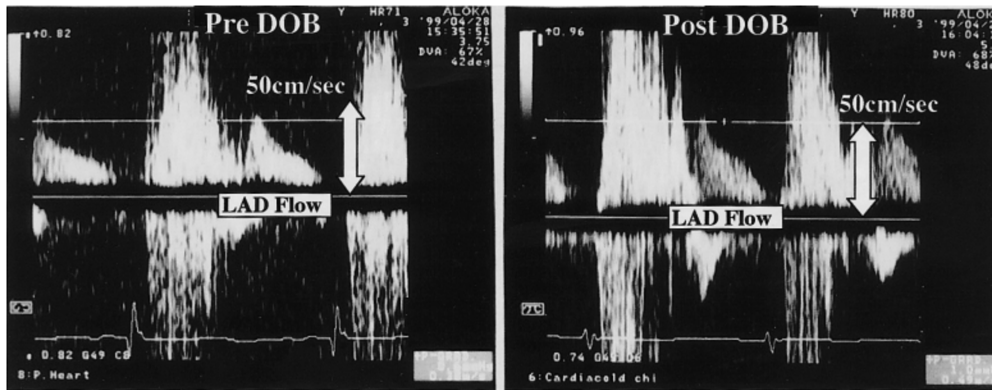

Fig. 1. LAD flow velocity assessed by transthoracic echocardiography. Left side: pre Dobutamine infusion. LAD flow velocity is 38 cm/seconds. Right side: post Dobutamine infusion. LAD flow velocity is 50 cm/seconds.

axillar pulse tracings was rate corrected to a heart rate of 60 beats/minute by dividing by the square root of the RR interval. Rate-corrected mean velocity of circumferential fiber shortening (mVcfc) was calculated as the shortening fraction divided by the rate-corrected ejection time. End-systolic wall stress (ESS) was calculated from Grossman et al. (1975): $ESS = 1.35 \times ESP \times ES/4 \times PWS (1 + PWS/ES)$, where ESP is the end-systolic pressure, LVES the end-systolic dimension, and PWS the posterior wall thickness at the end-systole. M-mode echocardiographic measurements were determined as the mean values for five cardiac cycles.

Coronary flow velocity measurements

Two-dimensional, color, and Doppler transthoracic echocardiography were performed using an Aloka SSD 5500 system with a 5.0 or 7.5 MHz transducer. Center frequency for B and M-mode was 10 MHz. At the setting of the pulse repetition frequency between 2.6 and 6.3 kHz and Doppler filter of 400 Hz, transducer was manipulated to obtain the short-axis view of the aortic valve, and Doppler color flow images were superimposed. The color gain was adjusted to provide the optimal images. Sample volume was decreased to the minimum possible. From the standard short-axis view of great vessels, the left main coronary artery could usually be recorded as it arises from the aorta. Visualization of the bifurcation of the left main artery into the LAD and circumflex branches could be accomplished by moving the transducer up one interspace and angling it inferiority. Occasionally, by assuming the long-axis view of the right ventricular outflow tract, the slight leftward inclination of the transducer beam provided an easier window to image the left main coronary artery and bifurcation of the LAD and circumflex branches. After adjusting the scanning plane so as to image the coronary artery as long as possible, the sample volume was positioned in the center of the lumen.

Measurements of peak velocity were performed using the internal analysis package of the ultrasound unit. Measurements were calculated considering the angle between the Doppler beam and the coronary flow direction as determined by the two-dimensional echocardiogram. Absolute velocity was defined as the product of the measured velocity and the cosine of the angle between the Doppler beam and the direction of blood flow. The ratio of CFV during dobutamine infusion to baseline CFV was calculated as an index of CFV response. Values for each parameters were obtained by averaging measurements from 5 consecutive cardiac cycles.

Statistics

All data are expressed as the mean±S.D. Paired t-test two-tailed used to compare the measurements obtained in the basal state and during dobutamine infusion. Correlations were sought using the least-square linear regression analysis. To evaluate the effects of observational variability on the measurement of LAD peak flow velocity and CFV response, two independent observers analyzed 10 randomly selected Doppler velocity recordings. Interobserver variability was calculated as the standard deviation of the differences between the two observers, expressed as a percent of the average value. Reproducibility was assessed in 10 children who underwent LAD flow measurements by Doppler echocardiography twice. A p-value < 0.05 was considered statistically significant.

RESULT

Dobutamine infusion could be completed without adverse effects, such as arrhythmia or hypotension, in all subjects. Adequate spectral Doppler recordings of LAD peak flow velocity for the assessment of CFV response were obtained in 26 of 30 patients (87%) before and during dobutamine infusion. The LAD flow tracings of 4 patients were excluded from the analysis because of overlapping wall noise and inability to determine entire spectral velocity envelope. Therefore, data were analyzed in 26 subjects.

All measurements for 26 subjects are shown in Table 1. After dobutamine infusion, heart rate, systolic blood pressure, end-systolic blood pressure, end-systolic wall thickness, and mVcfc increased significantly. Conversely, end-diastolic dimension, end-systolic dimension, and ESS decreased significantly. The magnitude of increase in mVcfc during dobutamine infusion was low in younger children and increased significantly with age ($r=0.61$, $p<0.001$). However, the percent decrease of ESS did not show a significant change with age.

At rest, the mean LAD peak flow velocity was 34 ± 8 cm/seconds and decreased significantly with age ($r=-0.69$, $p<0.001$). During dobutamine infusion, the LAD peak flow velocity increased significantly. No significant relationship between heart rate (HR) and resting LAD peak flow velocity was observed ($r=0.24$, $p=0.25$). A regression line between the LAD peak flow velocity during dobutamine infusion and age was less ($r=-0.40$, $p<0.05$) than that between the basal LAD peak flow velocity and age (Fig. 2). The

TABLE 1. *Data from patients before and during dobutamine infusion*

	Rest	Dobutamine	p-value
Heart rate (/minute)	95±24	103±23	<0.01
Systolic blood pressure (mmHg)	112±29	139±22	<0.0001
End-systolic pressure (mmHg/minute)	86±13	102±16	<0.0001
Rate-pressure product (mmHg/minute)	10 642±1970	14 318±2423	<0.0001
Left ventricular end-diastolic dimension (mm)	34±8	33±8	<0.05
Left ventricular end-systolic dimension (mm)	23±5	20±4	<0.0001
End-systolic wall thickness (mm)	8±2	10±3	<0.0001
Rate-corrected mean velocity of fiber shortening (/cir)	0.98±0.18	1.29±0.29	<0.0001
End-systolic wall stress (g/cm^2)	61±19	51±15	<0.0001
LAD peak flow velocity (cm/seconds)	34±8	47±7	<0.0001
LAD flow velocity response		1.43±0.27	

LAD, left anterior descending coronary artery.

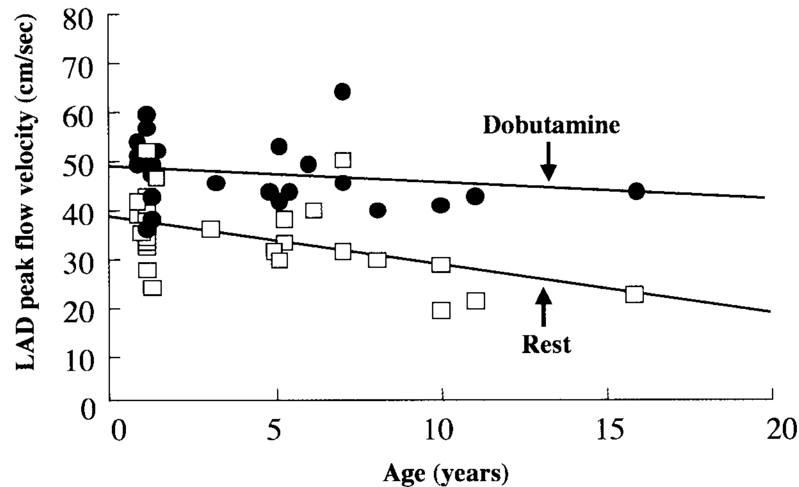

Fig. 2. Relationships between age and LAD peak flow velocity before (square mark; $r=-0.68$, $p<0.0001$) and during dobutamine infusion (circle mark; $r=-0.40$, $p<0.05$).

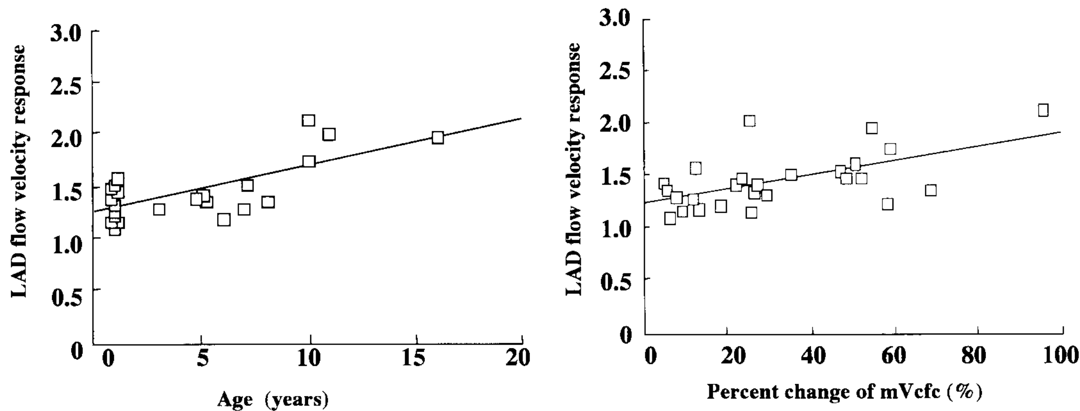

Fig. 3. Left: Relationships between age and LAD flow velocity response ($y=1.21+0.046X$, $r=0.75$, $p<0.0001$, $n=26$).
Right: Between percent change of mVcfc and LAD flow velocity response ($y=-1.22+0.66X$, $r=0.57$, $p<0.005$, $n=26$).

mean CFV response was calculated as 1.43 ± 0.27. The CFV response was low in the younger children and increased significantly with age ($r=0.75$, $p<0.0001$) (Fig. 3). The CFV response did not show significant relationships with the changes in heart rate ($r=0.12$, $p=0.55$), systolic blood pressure ($r=0.24$, $p=0.24$), or rate-pressure product ($r=0.27$, $p=0.19$) during dobutamine infusion. However, a significant relationship between the CFV response and the percent change of mVcfc was observed ($r=0.57$, $p<0.005$) (Fig. 3). The CFV response did not show a significant correlation with the percent change of ESS ($r=-0.12$, $p=0.58$) during dobutamine infusion.

There was a good agreement between the two independent observers' measurements for the LAD peak flow velocity and CFV response ($r=0.94$, $r=0.92$). Inter-observer variability for the LAD peak flow velocity and CFV response were 5.5% and 6.1%, respectively. Reproducibility for the LAD peak flow velocity and CFV response was 7.1% and 8.3%, respectively.

Discussion

Coronary flow has been difficult to study in children because of the lack of a reliable and noninvasive means of measuring coronary flow velocity. Recently, LAD peak flow velocity has been measured using transthoracic Doppler echocardiography in children (Noto et al. 1997; Jureidini et al. 1998; Harada et al. 1999). This noninvasive technique has been shown to reflect an invasive measurement of coronary flow velocity by Doppler guidewire method in adults (Hozumi et al. 1998; Harada et al. 2001a, b). Thus, using transthoracic Doppler echocardiography, we could assess the effects of inotropic stimulation on the LAD peak flow velocity and CFV response and their relations to age and LV contractility.

Previous studies in children have shown the effects of dobutamine on LV systolic performance (Colan et al. 1985; De Wolf et al. 1998a, b; Hozumi et al. 1998; Jureidini et al. 1998; Harada et al. 1999). In the present study, we demonstrated that low-dose dobutamine infusion increased the mVcfc, whereas ESS was reduced. Our results were consistent with those in previous reports. However, this response to dobutamie found in the present study was less sensitive in infants than in older children.

The cardiovascular system in infants is immature compared with that in elder children (Romero and Friedman 1979; Harada et al. 2000). Data from animal studies suggest that the immature cardiovascular system is less sensitive to dobutamine and that higher doses are required to achieve similar effect seen in mature animals (Gauthier et al. 1975; Driscoll et al. 1979). Perkin et al. (1982) also reported that infants younger than 12 months of age showed decreased responsiveness to dobutamine. These findings are similar to our results obtained in the present study.

The increased metabolic demand due to inotropic stimulation enhances coronary blood flow. In the present study, the LAD peak flow velocity increased during dobutamine infusion, however, the response to dobutamine was low in infants and increased with increasing age. Furthermore, the percent change of mVcfc during dobutamine infusion correlated with the CFV response, which indicates the dependence of contractile function on the level of myocardial blood flow as suggested previously (Lee et al. 1997; Harada et al. 2001b; Yasuoka et al. 2001). Our data provide evidence for an association between the CFV response and LV functional reserve during inotropic stimulation, but other factors may also be involved.

In the present study, dobutamine infusion increased in heart rate and systolic blood pressure as determinants of cardiac work. However, the percents of increase in heart rate, systolic blood pressure, and rate-pressure product during dobutamine infusion did not change with age or the CFV response. Thus, heart rate and systolic blood pressure might not be a cause of age-dependent of coronary flow response to dobutamine.

In the present study, resting CFV in infants was high as reported previously (Harada et al. 1999, 2001a, b; Yasuoka et al. 2001), which was consistent with data from experiments performed in sheep (Fisher et al. 1980, 1982). An increase in resting CFV has been demonstrated to be a main mechanism of restriction of coronary flow reserve (McGinn et al. 1990). Age-related changes in coronary flow reserve have been shown experimentally and clinically. Buss et al. (1987) have demonstrated that younger rabbits exhibited a smaller flow response to exogenous adenosine than older rabbits. The previous invasive study in children (Hamaoka et al. 1995) suggested that coronary flow reserve during adenosine infusion has a tendency to decrease with increasing age. Other investigators (Donnelly et al. 1998) have shown that maximal myocardial perfusion in infants was significantly less than that found in adults during adenosine infusion. On the basis

of these observations, the myocardial blood flow in infants may not be able to respond adequately on metabolic demand. Similar mechanisms may be operated during dobutamine infusion.

The present study has some important limitations. First, The population tested remains rather small. It was not available more children over all ages, especially neonates, because of the voluntary nature of participation of the subjects. Second, the subjects examined in the present study were not entirely normal. Children with a previous history of Kawasaki disease and normal epicardial coronary arteries have been reported to have reduced coronary flow reserve (Muzik et al. 1996). Although Iemura et al. (2000) showed that patients with Kawasaki disease who had normal coronary arteries in the acute phase have normal vascular wall morphology and vascular function, we have no data regarding this. Third, in the present study, the LAD peak flow velocities were calculated considering the angle between the Doppler beam and the coronary flow direction as determined by the two-dimensional echocardiogram. When the angle of incidence to flow is excessive, measurements of velocities may be unreliable. However, the ratio of maximal diastolic velocities during dobutamine infusion to those at control should not be affected by the angle of incidence, because the cosine factors of the numerator and denominator would be canceled out. For these reasons, LAD peak flow velocity recordings may be useful in expressing the ratios describing the differences in 2 states such as coronary flow reserve.

In the present study using high frequency transthoracic echocardiography, we demonstrated the age-related changes in CFV response and LV functional reserve with low-dose dobutamine infusion. Responses of LV contractility and coronary flow to low-dose dobutamine were less sensitive in infants and increased with increasing age.

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