〔千葉医学 77：133～144, 2001〕

〔Original Paper〕

Noninvasive Doppler echocardiographic assessment of left anterior descending coronary artery stenosis from flow velocity changes during dobutamine infusion : comparison with dipyridamole infusion

Rei Hasegawa, Kenji Fusejima, Masashi Suzuki, Yoichi Kuwabara and Yoshiaki Masuda

(Received November 26, 2000, Accepted January 12, 2001)

SUMMARY

To determine the feasibility of obtaining coronary flow measurements using transthoracic color Doppler echocardiography during dobutamine infusion, and to compare it with dipyridamole infusion, 58 patients underwent transthoracic color Doppler echocardiography. Coronary flow velocities in the mid-portion of left anterior descending artery (LAD) were recorded at the basal state and during dobutamine infusion (5-40 μg/kg/min) and during dipyridamole infusion (0.56 mg/kg). Coronary flow velocity ratio (CFVR) were calculated as the ratio of hyperemic mean diastolic flow velocity (MDV) to basal MDV. The detection rate for LAD flow in the dobutamine study was significantly smaller than that in the dipyridamole study (75.8 vs 89.4%). Coronary flow velocity of LAD clearly increased during dobutamine and dipyridamole infusion in patients without significant stenosis in LAD ($n=21$), whereas their increases were trivial in patients with significant stenosis ($n=23$). There were significant differences in CFVR between patients with and without significant coronary stenosis for either dobutamine or dipyridamole ($P<0.0001$). There was no significant difference in the sensitivity and specificity of CFVR for the presence of significant LAD stenosis among the groups receiving dipyridamole, dobutamine with 20 or dobutamine with 40 μg/kg/min. To predict the presence of significant LAD stenosis, 20 μg/kg/min of dobutamine is sufficient.

Key words : coronary flow reserve, dobutamine, echocardiography, coronary disease

3rd Department of Internal Medicine, School of Medicine, Chiba University, Chiba 260-8670.
長谷川玲, 伏島堅二, 鈴木 将, 桑原洋一, 増田善昭：経胸壁的カラードプラ法を用いた冠血流予備能計測による冠動脈病変の非侵襲的診断：ドブタミン負荷とジピリダモール負荷の比較検討.
千葉大学医学部内科学第三講座 Tel. 043-222-7171.
2000年11月26日受付, 2001年1月12日受理

I. Introduction

Recent technological advance in color Doppler echocardiography may provide a high success rate in measuring coronary flow velocity and noninvasive coronary flow velocity ratio (CFVR) assessment. It was reported that CFVR determined by transthoracic color Doppler echocardiography was useful in the noninvasive assessment of significant stenosis in left anterior descending artery (LAD)[1]. But LAD flow was only detectable by transthoracic color Doppler echocardiography, while the flow in left circumflex artery (LCX) and right coronary artery (RCA) could not be studied. It was necessary to detect wall motion abnormalities during pharmacological stress echocardiography for the diagnosis of significant stenosis in LCX and RCA.

Pharmacological stress echocardiography is playing an increasingly important role in the noninvasive diagnosis of coronary artery disease. In earlier reports, both dobutamine and dipyridamole stress echocardiography procedures have shown high sensitivity and specificity for the diagnosis of coronary artery disease. Dipyridamole stress echocardiography showed a greater accuracy for the diagnosis of multivessel disease, but a lower sensitivity for the detection of single vessel disease compared with dobutamine stress echocardiography[2-5]. Because of the higher sensitivity of new wall motion abnormality, dobutamine may prove superior to dipyridamole for detecting stenosis of the two vessels other than LAD.

During dobutamine stress echocardiography, not only wall motion assessment, but measurement of LAD flow velocity is also available by transthoracic color Doppler echocardiography. This combined method may be more sensitive for detecting coronary artery disease. However, the magnitude of coronary flow velocity increase induced by dobutamine infusion is unknown. Neither is it known whether assessment of CFVR by transthoracic color Doppler echocardiography during dobutamine infusion is as useful in the noninvasive assessment of significant stenosis in the LAD as dipyridamole.

The purposes of this study were to compare the feasibility of obtaining coronary flow measurements by transthoracic color Doppler echocardiography and the sensitivity and specificity for LAD stenosis during dipyridamole infusion and dubutamine infusion. Furthermore, this study attempted to determine the minimum dose of dobutamine needed to predict significant LAD stenosis.

II. Methods

Study Patients

We prospectively examined 58 consecutive patients (49 men, 9 women; mean age, 64± 9 years, range 41 to 77) undergoing coronary angiography for diagnostic purposes. All patients underwent Doppler echocardiographic studies within 7 days after coronary angiography. Patients were prospectively classified into two groups on the basis of LAD stenosis severity: 21 patients had a proximal LAD lumen diameter stenosis $>$ 70% (group A) and 23 had a proximal LAD lumen diameter stenosis $<$70% (group B). LAD stenosis ranged from 71% to 95% (mean 83.0±5.6%) in group A, and 0% to 68% (mean 44.6± 16.9%) in group B. Five patients had double vessel disease and 1 patient had triple vessel disease in group A, 3 patients had single vessel disease in group B. No patients had a spastic coronary artery, a long and tandem lesion, a diffuse stenosis, collateral flow to the stenosed artery, or evidence of thrombus. Patients with unstable angina, recent and old myocardial infarction, decompensated conges-

tive heart failure, atrial fibrillation, previous coronary bypass surgery, systemic hypertension, anemia (hemoglobin level <10.0 g/dl) were not enrolled. None had evidence of left ventricular hypertrophy (septal or posterior wall thickness >11mm) on echocardiographic examination. Antianginal medication was discontinued a minimum of 8 hours before the Doppler echocardiographic study. Only 2 patients were receiving a long-acting beta-adrenergic blocking agent. All patients gave informed consent to the protocol.

Doppler Echocardiographic Studies

Echocardiographic examinations were performed with a Toshiba SSA-380A digital ultrasound system with the center frequency of 5 MHz (Doppler frequency ; 5 MHz). In the measurement of LAD flow by color Doppler, the ultrasound beam was directed toward the heart from the left precordum through the third, fourth, and fifth intercostal spaces of the patient with lateral decubitus position. First, the left ventricle was imaged in long-axis echocardiographic sections and then the beam was inclined laterally to identify the anterior interventricular sulcus. Under color Doppler monitoring, the area of the anterior interventricular sulcus was carefully searched to identify a tubular structure (about 2 mm in diameter for the mid-portion of the LAD) containing characteristic Doppler flow signals. Its shape and position were then confirmed by the short-axis echocardiographic sections. The long-axis section was carefully adjusted to minimize the angle of incidence between the ultrasound beam and the longitudinal axis of LAD. When a diastolic circular color-coded blood flow was recognized, PW Doppler recording was attempted with the sample volume (2.0mm wide) positioning in diastole. The angle between color flow and ultrasound beam was corrected using the software package included in the ultrasound unit. Doppler of the LAD flow showed a characteristic biphasic flow pattern with a larger diastolic component and a small systolic one (Fig. 1). Generally, it was difficult to trace the LAD lumen continuously throughout a cardiac cycle on the same echocardiographic sections because the coronary artery moves constantly. Therefore, greater attention was focused on the event in diastole, although efforts were also made to visualize the event in systole by changing the echo section. In the late stage of dobutamine infusion, recordings were often difficult especially during systole because of hyperkinetic contraction. Therefore, evaluation of post-stenotic coronary flow kinetics in response to dobutamine infusion was made from the diastolic flow pattern. Real-time images were stored in cine loop memory, that permits frame-by-frame review, and were recorded on a videotape.

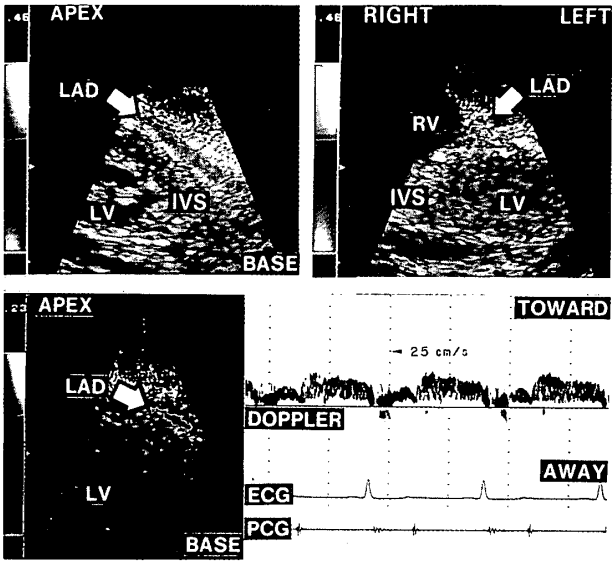

Fig. 1 Doppler flow signal in the left anterior descending artery. The long-axis echocardiographic section (left upper panel) and short-axis section (right upper panel). Placement of sample volume in the distal LAD (left lower panel) for the measurements coronary flow velocity in the LAD(right lower panel) in pulse Doppler flowmetry.

Coronary Flow Velocity Measurements during Dobutamine and Dipyridamole Infusion

Dipyridamole was intravenously infused at 0.56 mg/kg for 4 minutes. Blood pressure, heart rate and 12-lead electrocardiograms were monitored every minute before and during infusion and at recovery. Doppler evaluation of LAD post-stenotic flow velocity was obtained in the resting condition, every 2 minutes from starting dipyridamole injection and up to 10 minutes after dipyridamole infusion.

Dobutamine was infused with an infusion pump at an initial dose of 5 μg/kg/min for 4 minutes and the dose increased every 4 minutes to 10, 20, 30, and 40 μg/kg/min.

Blood pressure, heart rate and 12 lead ECG were recorded in the control basal period, every 2 min in each stage and recovery. Doppler evaluation of LAD post-stenotic flow velocity was made in the control state and in the last 1 min of every stage. Dobutamine infusion was discontinued if complex ventricular ectopic beats, systemic hypotension (systolic blood pressure $<$ 90 mmHg), severe hypertension (systolic blood pressure $>$ 220 mmHg or diastolic blood pressure $>$ 120 mmHg), heart rate $>$ 85% of the estimated peak maximal heart rate (220 - age in years), ST-segment shift $>$ 2 mm, or symptoms unacceptable by the patients, such as chest pain occured. The 2 tests were performed in random order on different days within 2 days.

Echocardiographic measurements

Coronary flow velocity assessment was carried out by one experienced echocardiographer blinded to the clinical and angiographic data. Measurements were made off-line using the computer incorporated in the ultrasound system. Mean diastolic flow velocity (MDV) was calculated by the area of the diastolic flow velocity divided by duration of the diastolic phase. Peak diastolic flow velocity (PDV) and MDV were measured during basal and hyperemia states in the dipyridamole study and in the basal state and during infusion of 20 and 40 μg/kg/min in the dobutamine study. Each parameter was averaged with the highest 3 cycles. The ratio of PDV and MDV at the hyperemic and basal states in the dipyridamole study was defined as CFVR(PDV) and CFVR(MDV). In the dobutamine study, CFVR was obtained at the stage of 20 and 40 μg/kg/min in the same way. CFVR with dipyridamole was $>$ 2.0 taken as normal based on the previous studies that evaluated post-stenotic flow velocities in LAD[6-7].

Coronary Angiography

Selective coronary angiography was performed by the Judkins technique in multiple projections and recorded on a cine film. Quantitative analysis was done with the Cardiovasucular Measurement System (CMS-MEDIS, Medical Imaging Systems) [8]. Stenosis was considered significant if there was$>$ 70 % lumen diameter narrowing in at least one projection.

Statistical Analysis

Continuous data are expressed as mean and standard deviation (SD). A paired Student t test was used to assess differences in variables from control period to hyperemia and with each of dobutamine dose within the group. The differences between the two groups for the parametric data were tested by the unpaired two-tailed t test. Chi-square analysis was used to assess differences in the detection rate for LAD flow and accuracy between dobutamine and dipyridamole. A p value $<$0.05 was considered statistically significant.

Ⅲ. Results

Under the guidance of color Doppler flow mapping, adequate spectral Doppler recordings of coronary flow were obtained in the mid-portion of LAD for the assessment at both baseline and stress in 52 out of 58 patients in the dipyridamole study (89.6%), and in 44 in the dobutamine study (75.8%), and were included in the further analysis. The detection rate for LAD flow in the dobutamine study was significantly smaller than that in the dipyridamole study ($P<0.05$), because of an increase in heart rate and contractility. No major adverse effects occurred in each study. Minor adverse effects in the dobutamine study included single premature ventricular contractions (2 patients), headache, and palpitation (1 patient) at 20 μg/kg/min. In the dipyridamole study, headache, flushing, palpitation, and nausea occurred in a patient, respectively.

Table 1 Hemodynamic changes induced by dipyridamole and dobutamine

	Group A ($n=21$)	Group B ($n=23$)	p
Dipydamole Control (cm/s)			
HR (beats/min)	67±11	65±11	NS
SBP (mmHg)	108±13	109±12	NS
DBP (mmHg)	59± 9	62±11	NS
Hyperemia			
HR (beats/min)	74±13	75±11	NS
SBP (mmHg)	96±21	101±13	NS
DBP (mmHg)	50± 7	53± 8	NS
Dobutamine Control (cm/s)			
HR (beats/min)	62±10	62±10	NS
SBP (mmHg)	119±14	112±16	NS
DBP (mmHg)	63±10	59±11	NS
Dobutamine 20 μg/kg/min			
HR (beats/min)	84±18*	90±21*	NS
SBP (mmHg)	131±20*	130±32*	NS
DBP (mmHg)	57±14	57±13	NS
Dobutamine 40 μg/kg/min			
HR (beats/min)	109±20*	119±21*	NS
SBP (mmHg)	142±11*	145±32*	NS
DBP (mmHg)	57±11	60±23	NS

*$P<0.005$ vs control state. Heart rate (HR) and diastolic (DBP) and systolic (SBP) blood pressures during the basal state and dipyridamole or dobutamine dosed state were not different between groups A and B.

Hemodynamics

The hemodynamic changes during dobutamine and dipyridamole infusion are shown in Table 1. During dipyridamole infusion, heart rate increased and systolic and diastolic blood pressures decreased in both groups A and B. Heart rate, systolic or diastolic blood pressures during the control period or hyperemia did not differ significantly between groups A and B. The maximal increase in LAD flow velocity was occurred at 6.4±1.7 min in group A, and 6.9±1.6 min in group B after the start of dipyridamole infusion.

During dobutamine infusion, patients of in both group A and B showed significant increases in heart rate and systolic blood pressure, but diastolic blood pressure did not change. Heart rate, systolic and diastolic blood pressures during the control period or 20 and 40 μg/kg/min of dobutamine were similar between groups A and B. Dobutamine was infused up to 40 μg/kg/min in all patients except 8 patients in group A because of chest pain in 4 and ST depression in 4 at the stage of 20 μg/kg/min. In group B, one patient complained headache and another patient complained palpitation at 30 μg/kg/min.

Coronary flow velocity changes during dobutamine and dipyridamole infusion

In patients of group B, coronary flow velocity of LAD clearly increased during dobuta mine and dipyridamole infusion (Fig. 2). By contrast, coronary flow velocity in LAD was only slightly altered by dobutamine and dipyridamole in group A patients (Fig. 3).

PDV and MDV at basal state were not different between groups A and B (27.4±9.6 vs 25.8±9.0 cm/s and 20.0±7.3 vs 17.6±5.6 cm/s) (Table 2). PDV and MDV increased

from control values during dipyridamole induced hyperemia in the patients of both groups A and B (40.5±16.9, 30.6±13.5 cm/s and 65.0±18.2, 46.7±13.9 cm/s, $P<0.0001$). However, PDV and MDV during hyperemia in group A were significantly lower than those in group B (40.5±16.9 vs 65.0±18.2 cm/s, $P<0.0001$ and 30.6±13.5 vs 46.7±13.9 cm/s, $P<0.001$). As a result, CFVR (PDV) and CFVR (MDV) were significantly lower in group A than group B (1.46±0.25 vs 2.66±0.75 and 1.53±0.27 vs 2.74±0.71, $P<0.0001$).

As in the dipyridamole study, PDV and MDV in dobutamine study were not different between groups A and B at the control state

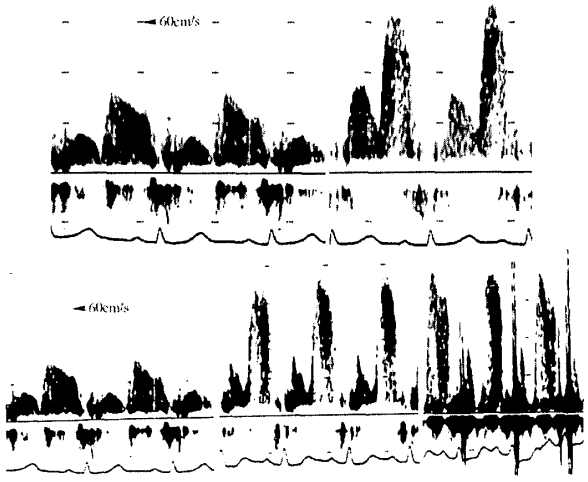

Fig. 2 Illustrative tracing in a patients without significant LAD stenosis. Upper panel, spectral Doppler flows at rest (left) and during hyperemia (right) after dipyridamole infusion. Lower panel, spectral Doppler flows at the control state (left) and during infusion of 20 μg/kg/min of dobutamine (middle) and 40 μg/kg/min (right) of dobutamine.

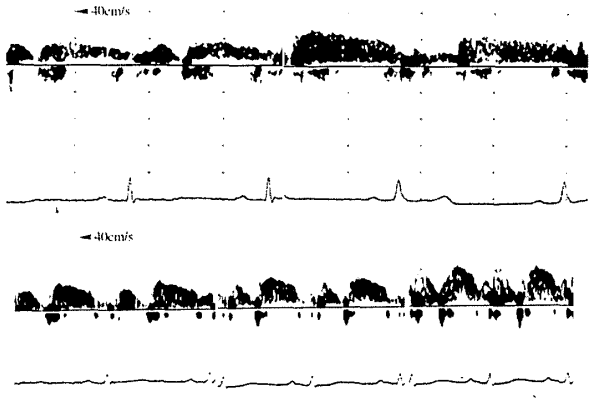

Fig. 3 Illustrative tracing in a patients with significant LAD stenosis. Upper panel, spectral Doppler flows at rest (left) and during hyperemia (right) after dipyridamole infusion. Lower panel, spectral Doppler flows at control (left) and at the stage of 20 μg/kg/min (middle) and at the stage of 40 μg/kg/min (right) during dobutamine infusion.

Table 2 Change in peak diastolic flow velocity and mean diastolic flow velocity induced by dipyridamole

Group	PDV (cm/s) Control	PDV (cm/s) Hyperemia	CFVR (PDV)	MDV (cm/s) Control	MDV (cm/s) Hyperemia	CFVR (PDV)
		*†	†		*※	†
A ($n=21$)	27.4±9.6	40.5±16.9	1.46±0.25	20.0±7.3	30.6±13.5	1.53±0.27
		*			*	
B ($n=23$)	25.8±9.0	65.0±18.2	2.66±0.75	17.6±5.6	46.7±13.9	2.74±0.71

*$P<0.0001$ vs basal state. †$P<0.0001$, ※$P=0.0004$ vs group B. LAD, left anterior descending coronary artery; PDV, peak diastolic velocity; MDV, mean diastolic velocity.

Table 3 Changes in peak diastolic flow velocity, mean diastolic flow velocity and coronary flow velocity ratio induced by dobutamine

	Group A ($n=21$)	Group B ($n=23$)	p
Control (cm/s)			
PDV	27.7±8.6	26.8±8.1	NS
MDV	20.7±6.3	18.1±5.4	NS
Dobutamine 20 μg/kg/min			
PDV	37.1±17.6†	58.8±20.1*	0.0005
CFVR (PDV)	1.31±0.31	2.26±0.62	<0.0001
MDV	26.3±10.9※	41.9±12.9*	0.0001
CFVR (MDV)	1.26±0.37	2.33±0.54	<0.0001
Dobutamine 40 μg/kg/min			
PDV	41.5±22.4	73.5±24.4*	0.0006
CFVR (PDV)	1.50±0.42	2.95±1.24	0.0003
MDV	30.8±17.9	51.2±18.0*	0.0027
CFVR (MDV)	1.49±0.52	2.87±1.12	0.0002

*$P<0.0001$, †$P=0.001$, ※$P=0.004$ vs control state. LAD, left anterior descending coronary artery; PDV, peak diastolic velocity; MDV, mean diastolic velocity; CFVR, coronary flow velocity ratio.

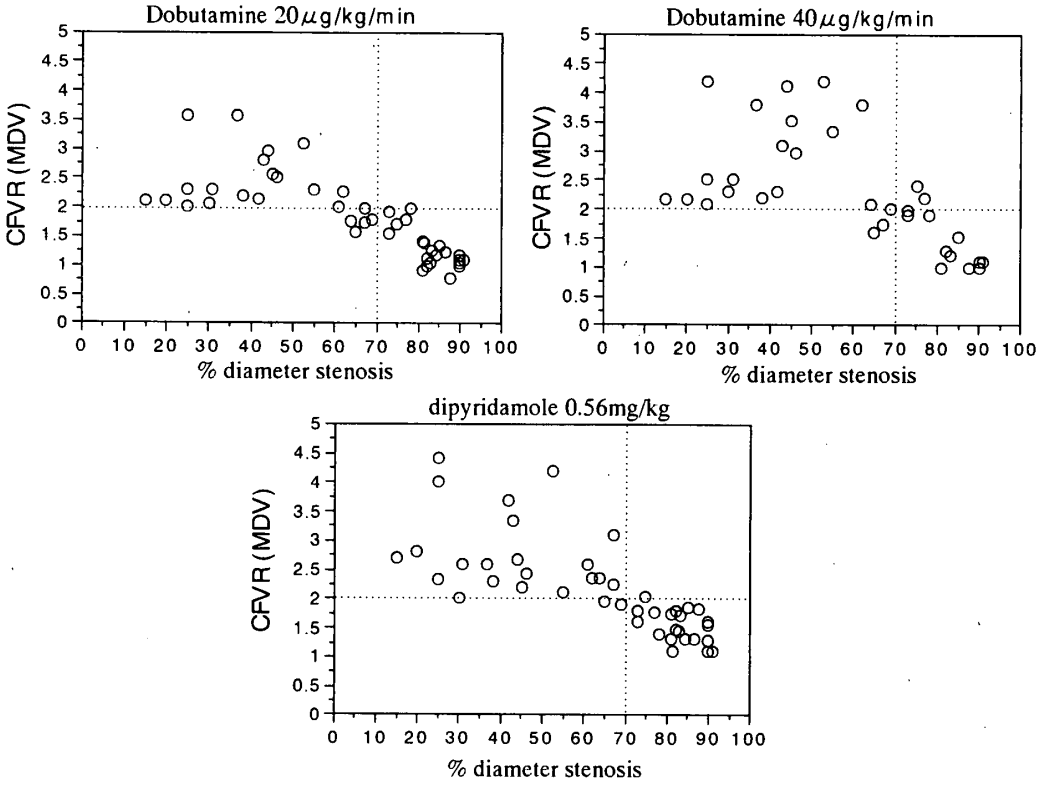

Fig. 4 Relationship between CFVR (MDV) with dipyridamole or dobutamine and percent diameter stenosis of LAD. Upper left panel, relation between CFVR (MDV) with dobutamine 20 μg/kg/min and percent diameter stenosis of LAD. A CFVR (MDV) with dobutamine 20 μg/kg/min < 2.0 predicts significant LAD stenosis (> 70% diameter stenosis) with a sensitivity and specificity of 100% and 78%. Upper right panel, relation between CFVR (MDV) with dobutamine 40 μg/kg/min and percent diameter stenosis of the LAD. A CFVR(MDV) with dobutamine 40 μg/kg/min < 2.0 predicts significant LAD stenosis with a sensitivity and specificity of 84% and 90%. Lower panel, relation between CFVR (MDV) with dipyridamole and percent diameter stenosis of LAD. A CFVR (MDV) with dipyridamole < 2.0 predicts significant LAD stenosis with a sensitivity and specificity of 95% and 91%.

(27.7±8.6 vs 26.8±8.1 cm/s and 20.7±6.3 vs 18.1±5.4 cm/s)(Table 3). In patients of group B, PDV and MDV clearly increased with dobutamine 20 and 40 μg/kg/min (58.8±20.1, 41.9±12.9 cm/s and 73.5±24.4, 51.2±18.0 cm/s, $P<0.0001$). However, PDV and MDV at the stage of 20 and 40 μg/kg/min of dobutamine in group A were significantly smaller than those in group B (37.1±17.6 vs 58.8±20.1, 26.3±10.9 vs 41.9±12.9 cm/s and 41.5±22.4 vs 73.5±24.4, 30.8±17.9 vs 51.2±18.0 cm/s, $P<0.001$). CFVR(PDV) and CFVR(MDV) with 20 and 40 μg/kg/min of dobutamine in group A were significantly lower than those in group B (1.31±0.31 vs 2.26±0.62, 1.26±0.37 vs 2.33±0.54 and 1.50±0.42 vs 2.95±1.24, 1.49±0.52 vs 2.87±1.12, $P<0.0001$).

Dipyridamole versus Dobutamine

The relationship between CFVR(MDV) and percent diameter stenosis is shown in Fig. 4. If a CFVR(MDV) at 20 μg/kg/min of dobutamine < 2.0 is defined as abnormal, it had a sensitivity of 100%, a specificity of 78%, and an accuracy of 88% for the presen-

ce of significant LAD stenosis.. A CFVR (MDV) at 40 μg/kg/min of dobutamine <2.0 had a sensitivity of 84%, a specificity of 90%, and an accuracy of 88%. In the dipyridamole study, a CFVR(MDV) <2.0 had a sensitivity of 95%, a specificity of 91%, and an accuracy of 93% for the presence of significant LAD stenosis. There was no significant difference in the sensitivity, specificity, and accuracy between dipyridamole, dobutamine 20 and 40 μg/kg/min.

The angle between Doppler beam and longitudinal axis of LAD

The angle between the Doppler beam and the longitudinal axis of LAD did not change significantly from the control state during dobutamine or dipyridamole infusion. The angle in the dobutamine study was 37.9±8.6 degrees in group A, 37.4±8.1 degrees in group B, and in the dipyridamole study 39.3±8.0 degrees in group A and 36.6±9.3 degrees in group B.

Ⅳ. Discussion

In this study, transthoracic color Doppler echocardiography during dobutamine infusion was shown to be as safe and feasible for noninvasive measurement of CFVR and detection of LAD stenosis as with dipyridamole.

Coronary flow velocity changes by dobutamine were clearly different. In patients without significant stenosis of LAD, coronary flow velocity of LAD definitely increased. By contrast, in patients with significant stenosis of LAD, the coronary flow velocity pattern of LAD was only minimally altered. And this reaction was similar to dipyridamole.

The mechanisms of augmentation in coronary flow are distintly different between dobutamine and dipyridamole. Dobutamine increases myocardial metabolic demand by enhancing contractility and increasing heart rate by stimulating β1-receptor. The increased metabolic demand results in secondary coronary vasodilation and coronary flow enhancement. Although dobutamine has an effect on coronary constriction by activation of beta2- and alpha-receptors, its vasodilating effect through metabolic demand are more pronounced. Dipyridamole dilates the coronary vasculature by increasing interstitial concentrations of adenosine, a potent coronary vasodilator.

Coronary flow velocity increase induced by 20 μg/kg/min of dobutamine was smaller than dipyridamole (0.56 mg/kg), as reflected by CFVR(MDV) in group B. CFVR (MDV) with 40 μg/kg/min of dobutamine had close agreement with that of dipyridamole. But there was no significant difference in the senitivity, specificity or accuracy among dobutamine 20 μg/kg/min, 40 μg/kg/min and dipyridamole for significant LAD stenosis. Thus, to predict the presence of significant LAD stenosis during dobutamine infusion, 20 μg/kg/min of dobutamine may be the sufficient dose.

CFVR measurements

There are significant limitations in predicting the hemodynamic significance by angiographic assessment of coronary artery stenosis. Coronary flow reserve (CFR) may be more accurate for detecting hemodynamic ally significance of coronary artery stenosis [9-14]. everal invasive methods of coronary flow velocity measurements using Doppler catheter or Doppler guide wire[6,7,15-19] have been established. Several studies have reported that transesophageal Doppler echocardiography is also useful in the assessment of coronary flow[20-22]. Transesophageal Doppler echocardiography allows for high resolution

images of the proximal LAD with coronary flow velocity by PW Doppler. However, it allows for only prestenotic flow in LAD, and is relatively invasive. Positron emission tomography has been applied to measure CFR in myocardium. Although this method is nonivasive, it is expensive and not widely available. Transthoracic color Doppler echocardiography is noninvasive, relatively inexpensive, and widely used in the clinical setting [23-27]. It was already reported that CFVR determined by transthoracic color Doppler echocardiography was useful in the assessment of LAD stenosis, accurately reflecting CFVR measured by invasive methods[1,28].

Combination of wall motion analysis and Doppler measurement of coronary flow in dobutamine stress echocardiography

Vasodilators such as dipyridamole or papaverine are usually used in CFVR measurements by Doppler technique, because their detection rate for LAD is higher than that of dobutamine. But only LAD flow can be detected by transthoracic color Doppler echocardiography, and the flow in the other two coronary vessels is difficult to recognize. Therefore, detecting of new wall motion abnormalities during pharmacological stress is helpful in diagnosis of significant stenosis in the other coronary vessels than LAD.

Dipyridamole stress echocardiography was first reported by Picano et al in 1985[29]. In many previous studies, although it was accurate for the diagosis of multivessel disease, only low sensitivity was available in detection of single vessel disease. To overcome this limitation, high dose dipyridamole (0.84 mg/kg) and atropine (0.25 to 1.0 mg) [30]have been tried. But the sensitivity in high dose dipyridamole (0.84 mg/kg) was 74%, and only 50% for single vessel disease [31].

Dobutamine stress echocardiography has high sensitivity in detecting coronary artery stenosis. Its overall sensitivity in previous reports was 80%, respectively[31]. Because of higher sensitivity for wall motion abnormality, dobutamine infusion is better when combining the Doppler technique and wall motion analysis. Stoddard et al.[20]reported that transesophageal Doppler echocardiography during dobutamine infusion could be used to assess CFVR in the LAD and that the assessment CFVR by transesophageal Doppler echocardiography was more sensitive than evaluation of left ventricular wall motion for LAD stenosis. This study supports the hypothesis. Therefore, the sensitivity of coronary artery disease may be improved by combination of Doppler flow and systolic function analysis during dobutamine infusion.

Limitations of the study

1) Coronary flow measurements except LAD could not be assessed in the present study.

2) Transthoracic Doppler echocardiography measures coronary flow velocity, not coronary blood flow. However, it has been reported that changes in coronary flow velocity induced by coronary vasodilators closely reflect changes in coronary blood flow.

3) We measured CFR only from diastolic mean velocities, not from mean velocities throughout the entire cardiac cycle, since obtaining complete Doppler spectral envelopes throughout the entire cardiac cycle is difficult due to cyclic cardiac motion. However, in the previous studies, the ratio of hyperemic to basal MDV and PDV was useful in the evaluation of functional coronary stenosis.

4) The factors that independently influence CFVR such as left ventricular hypertrophy, heart rate, coronary perfusion pressure, vent-

ricular preload, contractility, recent myocardial infarction, treatment receiving and measurement technique may influence CFVR in addition to coronary artery stenosis. These additional factors need attention when attempting to assess hemodynamic significance of coronary stenosis by CFVR measurements.

V. Conclusions

Coronary flow velocity measurements of LAD using transthoracic color Doppler echocardiography was safe and feasible during dobutamine infusion. Sensitivity and specificity of CFVR for dobutamine were similar to dipyridamole, and they were unchanged when dobutamine was infused by 20 or 40 $\mu g / kg / min$. To predict the presence of significant LAD stenosis by dobutamine transt horacic color Doppler echocardiography, 20 $\mu g/kg/min$ was thought to be a sufficient dose.

要　旨

ドブタミン(DOB)に対する冠血流速度の反応を明らかにするためにDOBを負荷し経胸壁カラードプラ法を用いて左前下行枝（LAD）の血流速度を計測し，検出率，血流速度変化率をジピリダモール（DIP）負荷した場合と比較した。血流速度変化率によるLAD狭窄病変の診断について感度，特異度を両薬剤で比較し，更に狭窄病変の診断に必要なDOBの最低負荷量を検討した。

対象は狭心症58例。DOBは最高40γまで投与し負荷前，20，40γ時にLAD血流速度を計測した。血流波形より拡張期最高流速（PDV），拡張期平均流速（MDV）を計測し，負荷後値を負荷前値で除して冠血流速度変化率（CFVR）を算出した。DIPは0.56㎎/㎏を4分間で投与し，2分毎にLAD血流速度を計測し同様に冠血流予備能（CFR）を算出した。

血流検出率はPER負荷89%，DOB負荷75%であった。冠動脈造影より70%以上の有意狭窄例21例（A群）と70%未満の非有意狭窄例23例（B群）に分類した。DOB，DIP負荷ともA群では血流速度の増加は軽度であったが，B群では著明に増加した。A群のCFR，CFVRはB群より有意に小さかった。CFR＜2.0を基準とするとLAD70%狭窄に対する感度95%，特異度91%であった。CFVR＜2.0を基準とするとDOB20γでは感度100%，特異度78%で，DOB40γでは感度84%，特異度85%であった。DIPとDOB20，40γの狭窄病変診断の間に感度，特異度の有意差は認めなかった。

経胸壁的カラードプラ法を用いたLADの血流速度計測はDOB負荷時にも十分可能であった。DOB負荷は検出率ではDIP負荷に劣るが，狭窄病変の診断については同等であった。狭窄病変の診断はDOB20γまでの比較的低負荷量でも十分可能であった。

References

1) Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, Morioka S. Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. Circulation 1998; 97: 1557-62.

2) Previtali M, Lanzarini L, Ferrario M, Tortorici M, Mussini A, Montemartini C. Dobutamine versus dipyridamole echocardiography in coronary artery disease. Circulation 1991; 83 [suppl III]: III27-III31.

3) Beleslin B, Ostjic M, Stepanovic J, Diordjevic-Dikic A, Stojkovic S, Nedeljkovic M, Stankovic G, Petrasinovic Z, Gojkovic L, Vaslijevic-Pokrajcic Z, Nedeljkovic S. Stress echocardiography in the detection of myocardial ischemia. Circulation 1994; 90: 1168-76.

4) Previtali M, Lanzarini L, Fetiveau R, Poli A, Ferrario M, Falcone C, Mussini A. Comparison of dobutamine stress echocardiography, dipyridamole stress echocardiography and exercise stress testing for diagnosis of coronary artery disease. Am J Cardiol 1993; 72: 865-70

5) Dagianti A, Penco F, Agati L, Sciomer S, Rosanio S, Fedele F. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 1995; 26: 18-25.

6) Miller DD, Donohue TJ, Younis LT, Bach RG, Aguirre FV, Wittry MD, Goodgold HM, Chaitman BR, Kern MJ. Correlation of pharmacological ^{99m}Tc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenosis. Circulation 1994; 89: 2150-60.

7) Voudris V, Manginas A, Vassilikos V, Koutelou M, Kantzis J, Cokkinos DV. Coronary flow velocity changes after dipyridamole infusion: measurements using intravascular Doppler guide wire. J Am Coll Cardiol 1996; 27: 1148-55.

8) Hasse J, van der Linden MM, Di Mario C, van der Giessen WJ, Foley DP, Serruys

PW. Can the same edge-detection algorithm be applied to on-line analysis system? Am Heart J 1993; 126: 312-21.
9) Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol 1974; 33: 87-94.
10) Gould KL, Lipscomb K. Effects of coronary stenosis on coronary flow reserve and resistance. Am J Cardiol 1974; 34: 48-55.
11) Marcus ML, Wight C, Doty D, Eastham C, Laughlin D, Krumm P, Fastenow C, Brody M. Measurements of coronary velocity and reactive hyperemia in the coronary circulation of humans. Circ Res 1981; 49: 877-90.
12) Hoffman JIE. Maximal coronary flow and the concept of coronary vascular reserve. Circulation 1984; 70: 153-9.
13) Marcus ML, Wilson RF, White CW. Methods of measurement of myocardial blood flow in patients: a critical review. Circulation 1987; 76: 245-53.
14) Klocke FJ. Measurements of coronary flow reserve: defining pathology versus making decisions about patient care. Circulation 1987; 76: 1183-9.
15) Segal J, Kern MJ, Scott NA, King SB III, Doucette JW, Heuser RR, Ofili E, Siegel R. Alterations or phasic coronary artery flow velocity in humans during percutaneous coronary angioplasty. J Am Coll Cardiol 1992; 20: 276-86.
16) Doucette JW, Corl D, Payne GM, Flynn E, Goto M, Nassi M, Segal J. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. Circulation 1992; 85: 1899-911.
17) Ofili EO, Kern MJ, Lavovitiz AJ, St Vrain JA, Segal J, Aguirre FV, Castello R. Analysis of coronary blood flow velocity dynamics in angiographically normal and stenosed arteries before and after endolumen enlargement by angioplasty. J Am Coll Cardiol 1993; 21: 308-16.
18) Joye JD, Schulman DS, Lasorda D, Farah T, Donohue BC, Reichek N. Intracoronary Doppler guide wire versus stress single-photon emission computed tomographic thallium-201 imaging in assessment of intermediate coronary stenoses. J Am Coll Cardiol 1994; 24: 940-7.
19) Akasaka T, Yoshikawa J, Yoshida K, Maeda K, Hozumi T, Nasu M, Shomura T. Flow capacity of internal mammary artery grafts: early restriction and later improvement assessed by Doppler guide wire: comparison with saphenous vein grafts. J Am Coll Cardiol 1995; 25: 640-7.
20) Stoddard M, Prince C, Morris G. Coronary flow reserve assessment by dobutamine transesophageal Doppler echocardiography. J Am Coll Cardiol 1995; 25: 325-32.
21) Iliceto S, Marangelli V, Memmola C, Rizzon P. Transesophaeal Doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilation. Circulation 1991; 83: 61-9.
22) Redberg RF, Sobol Y, Chou TM, Malloy M, Kumar S, Botvinick E, Kave J. Adenosine-induced coronary vasodilation during transesophgeal Doppler echocardiography: rapid and safe measurement of coronary flow reserve ration can predict significant left anterior descending coronary stenosis. Circulation 1995; 92: 190-6.
23) Fusejima K. Noninvasive measurement of coronary artery blood flow using combined two-dimensional and Doppler echocardiography. J Am Coll Cardiol 1987; 10: 1024-31.
24) Fusejima K, Takahara Y, Sudo Y, Murayama, Masuda Y, Inagaki Y. Comparison of coronary hemodynamics in patients with internal mammary artery and saphenous vein coronary artery bypass grafts: a noninvasive approach using combined two-dimensional and Doppler echocardiography. J Am Coll Cardiol 1990; 15: 131-9.
25) Ross JJ Jr, Mintz RG, Chandrasekaran K. Transthoracic two-dimensional high frequency (7.5MHz) ultrasonic visualization of the distal left anterior coronary artery. J Am Coll Cardiol 1990; 15: 373-7.
26) Kenny A, Shapiro LM. Transthoracic high-frequency two-dimensional echocardiography, Doppler and color flow mapping to determine anatomy and blood flow patterns in the distal left anterior descending coronary artery. Am J Cardiol 1992; 69: 1265-8.
27) Kenny A, Wisbey CR, Shapiro LM. Measurement of left anterior descending coronary artery flow velocities by transthoracic Doppler ultrasound. Am J Cardiol 1994; 73: 1021-2.
28) Hozumi T, Yoshida K, Akasaka T, Asami Y, Ogata Y, Takagi T, Kaji S, Kawamoto T, Morioka S. Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by Doppler echocardiography: comparison with invasive technique. J Am Coll Cardiol 1998; 32: 1251-9.

29) Picano E, Distante A, Masini M, Morales MA, Lattanzi F, L Abbate A. Dipyridamole-echocardiography test in effort angina pectoris. Am J Cardiol 1985; 56: 452-6.
30) Picano E, Pingitore A, Conti U. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dipyridamole echocardiography. Eur Heart J 1993; 14: 1216-22.
31) Picano E, Lattanzi F, Masini M, Distante A, L Abbate A. High dose Dipyridamole echocardiography test in effort angina pectoris. J Am Coll Cardiol 1986; 8: 848-54.
32) Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997; 30: 595-606.