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Assessment of Coronary Flow Reserve with Transthoracic Doppler Echocardiography: Comparison with Intracoronary Doppler Method

To evaluate the feasibility and usefulness of transthoracic Doppler echocardiography (TTDE) as a non-invasive method in recording distal anterior descending (LAD) coronary flow velocity, we compared coronary flow reserve (CFR) measured by TTDE with measurements by intracoronary Doppler wire (ICDW). Twenty-one patients without LAD stenosis were studied. ICDW performed at baseline and after intracoronary injection of 18 μg adenosine. TTDE was performed at baseline and after intravenous adenosine (140 μg/kg/min for 2 min). Adequate Doppler recordings of coronary flow velocities during systole were obtained in 14 of 21 study patients (67%) and during diastole in 17 (81%) patients. Baseline and hyperemic peak diastolic flow velocities measured by TTDE were significantly smaller than those obtained by ICDW ($p<0.05$). However, diminishing trends of diastolic and systolic velocity ratio after hyperemia were similarly observed in both methods. CFR obtained by TTDE (3.0±0.5), was higher than the value calculated by ICDW (2.5±0.4). There were significant correlations between the values obtained by the two methods (r=0.72, $p<0.01$). It is concluded that TTDE is a feasible method in measuring coronary flow velocity and appears to be a promising non-invasive method in evaluating CFR.

Key Words : *Coronary Artery Disease; Echocardiography; Ultrasonography, Doppler; Circulation, Coronary*

Soo Mi Kim, Wan Joo Shim, Hong Euy Lim, Gyo Seung Hwang, Woo Hyuk Song, Do Sun Lim, Young Hoon Kim, Hong Seog Seo, Dong Joo Oh, Young Moo Ro

Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

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Address for correspondence
Wan Joo Shim, M.D.
Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine, 126-1, Anam-dong 5-ga, Sungbuk-gu, Seoul 136-705, Korea
Tel : +82.2-920-5445, Fax : +82.2-927-1478
E-mail : wjshimmd@unitel.co.kr

INTRODUCTION

Coronary flow reserve (CFR) is considered as an important diagnostic index of the functional significance of coronary artery stenosis (1-6). It is also employed in the evaluation of microcirculatory function of coronary circulation in conditions such as syndrome X and left ventricular hypertrophy (7, 8). Most CFR measurements utilize invasive techniques with a Doppler guide wire, which is available only during cardiac catheterization. As a non-invasive method, transesophageal Doppler echocardiography has been reported to be useful in assessing the significant left anterior descending artery (LAD) stenosis (9-14). However, transesophageal Doppler echocardiography is not completely noninvasive and can obtain only blood flow velocity of proximal LAD. With new ultrasonic technology, noninvasive measurement of the distal LAD flow by transthoracic high-frequency Doppler ultrasound is possible and several studies have reported the feasibility of the tests (15-19). But clinical usefulness and validation of TTDE in assessing CFR has not been fully determined (20, 21).

Therefore, the purpose of the study was to evaluate the feasibility of transthoracic Doppler echocardiography in recording coronary flow velocity as well as to validate CFR measurement by TTDE by comparing the value of CFR obtained by intracoronary Doppler wire method.

MATERIALS AND METHODS

Subjects

We prospectively examined 21 patients (10 males, 11 females; mean age 54.8±10.4 years). Coronary angiography was performed to evaluate atypical chest pain in 18 patients and follow up was done after percutaneous coronary angioplasty in three patients with pervious myocardial infarction. There were no significant LAD stenoses shown by coronary angiography. The patients with atrial fibrillation or more than second degree atrioventricular block were excluded from this study. Transthoracic and intracoronary Doppler measurement was done 1 day apart.

Intracoronary Doppler wire (ICDW)

A Doppler guide wire (0.014 inch, 14 MHz transducer, FloWire, Cardiometrics Inc., Mountain View, CA, U.S.A.) was advanced into the mid-part of the LAD. Doppler velocity profiles were displayed and an automated tracking algorithm was used to detect the peak instantaneous flow velocity and compute average peak velocity over two heart cycles as an index of coronary flow ratio. Peak Doppler flow velocities were obtained at baseline and after coronary hyperemia induced by intracoronary bolus injection of 18 μg adenosine. Coronary flow reserve was calculated as the ratio of hyperemic to baseline average peak velocity. Systolic, diastolic, and mean arterial pressures and heart rate were recorded on a multichannel recorder (Flomap II5600, Cardiometrics) during baseline conditions and 20 sec after intracoronary injection of adenosine.

Transthoracic Doppler echocardiography (TTDE)

Transthoracic Doppler echocardiography was performed by an operator with a high resolution ultrasound system (Sequoir 256, Acuson, Mountainview, CA, U.S.A.) with a 5 MHz transducer. The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. Long axis views of the left ventricle were obtained, and the ultrasound beam was then angled laterally and superiorly to image the anterior interventricular groove. Next, coronary blood flow in the distal portion of the LAD was examined with the help of color Doppler flow mapping (Fig. 1).

A sample volume was positioned on the color signal in the LAD, and Doppler spectral tracings of flow velocity were recorded. The spectral Doppler of LAD flow showed a characteristic biphasic flow pattern with a larger diastolic component and a small systolic one. We first recorded baseline spectral Doppler signals in the distal portion of the LAD. 140 μg/kg/min adenosine, a coronary vasodilator, was administered intravenously for 2 min. Doppler signals were continuously recorded at baseline and during the period of adenosine infusion. Measurements of hyperemic coronary velocity was done at the last 30 sec of adenosine infusion. All studies were recorded on 0.5 inch VHS videotape for off-line analysis. Continuous ECG monitoring was done during the study and blood pressure was recorded at baseline and at the peak effects of adenosine infusion.

Each study was analyzed by an investigator who was unaware of the Doppler wire data. Measurements were performed off-line by tracing the contour of the spectral Doppler signal, using the computer incoporated in the ultrasound system. Mean and peak, diastolic and systolic velocities were measured at baseline and peak hyperemic condition. An average of the measurements was obtained in three cardiac cycles. Coronary flow reserve was calculated as the ratio of hyperemic to basal mean diastolic

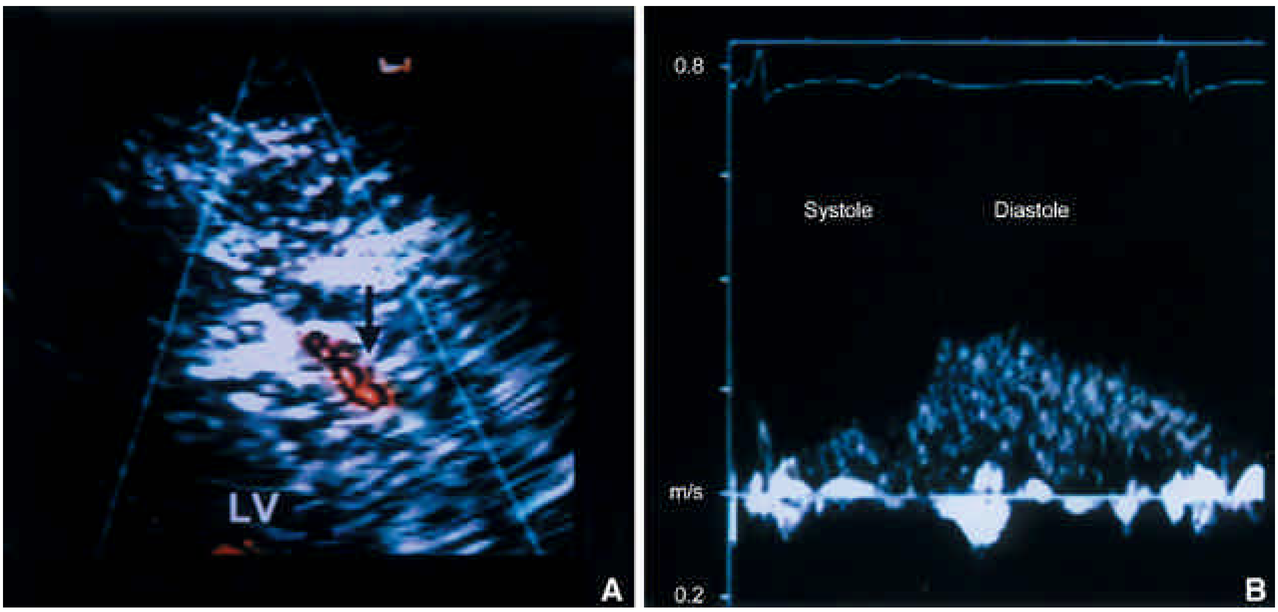

Fig. 1. A: Transthoracic color Doppler echocardiography shows blood flow of distal portion of the left anterior descending artery (LAD) in anterior interventricular groove (arrow). **B:** Blood flow in the distal LAD exhibits a characteristic biphasic coronary flow pattern, consisting of systolic and diastolic phases with higher velocity during diastole. LV, left ventricle.

coronary flow velocity.

Coronary angiography

Coronary angiography was performed by the Judkins technique. Two to three orthogonal projections were obtained, using a biplane angiography system. Coronary stenosis was evaluated using multiple projections by an experienced investigator unaware of the echocardiographic data.

Data analysis

Data are expressed as mean±SD. The differences between the two groups were tested by unpaired two-tailed t-test. Difference between baseline and hyperemic data within the two groups were tested by a paired two-tailed Student's t-test. Results of TTDE and ICDW for coronary flow reserve calculation were compared by linear regression analysis. Statistical significance was considered at p value of <0.05.

RESULTS

Adequate spectral Doppler recordings of diastolic flow for analysis were obtained in 17 of 21 study patients (81%), whereas systolic flow velocity were obtained in 14 patients (67%) by transthoracic Doppler echocardiography. One patient experienced severe chest pain and headache by intravenous adenosine infusion, thus the test was prematurely terminated. Another two patients experienced facial flushing during adenosine infusion but was able to tolerate the infusion.

Hemodynamics

Hemodynamic data before and after vasodilator application are shown in Table 1. Baseline heart rate were similar between the two methods (p=n.s). Baseline blood pressure was lower in TTDE than ICDW ($p<0.05$). Heart rate increased from 69±8/min to 80±11/min ($p<0.05$) and mean blood pressure decreased from 88±11 mmHg to 80±8 mmHg after intravenous adenosine infusion ($p<0.05$). Heart rate and mean BP were not significantly changed during intracoronary adenosine infusion.

Coronary flow velocity

An example of coronary flow velocity recordings obtained by TTDE and ICDW in the same patient is shown (Fig. 2). Mean baseline and hyperemic peak diastolic flow velocity measured by TTDE were significantly smaller than those obtained by ICDW ($p<0.05$, Table 2). However, trends in diminishing diastolic and systolic

Table 1. Hemodynamic data before and after adenosine infusion

No.	Age (year)	Sex	HR (bpm)				BP (mmHg)			
			TTDE		ICDW		TTDE		ICDW	
			Baseline	Hyperemia	Baseline	Hyperemia	Baseline	Hyperemia	Baseline	Hyperemia
1	28	m	64	79	63	65	85	75	83	79
2	62	m	63	65	69	70	110	87	105	93
3	70	f	78	84	67	63	90	80	96	91
4	46	m	61	80	66	68	107	97	116	112
5	51	f	67	70	71	74	87	87	107	106
6	67	f	70	71	63	61	82	73	98	90
7	58	f	75	96	58	61	80	74	95	85
8	58	f	56	65	80	82	83	73	101	97
9	61	f	72	88	80	81	97	85	86	84
10	45	f	67	90	75	77	93	82	93	91
11	58	f	62	68	75	76	97	87	137	130
12	48	f	79	96	90	93	97	93	109	106
13	54	f	65	83	67	69	87	73	95	87
14	62	f	70	88	93	96	77	70	130	121
15	51	m	76	76	60	62	80	78	77	75
16	43	m	88	100	68	75	75	73	78	71
17	68	m	59	71	60	61	83	82	106	97
Mean			69	80*	70	72	88†	80*,†	100	95
SD			8	11	10	10	11	8	16	15

ICDW, intracoronary Doppler wire; TTDE, transthoracic Doppler echocardiography; BP, blood pressure

*$p<0.05$ as compared to baseline, †$p<0.05$ as compared to intracoronary study

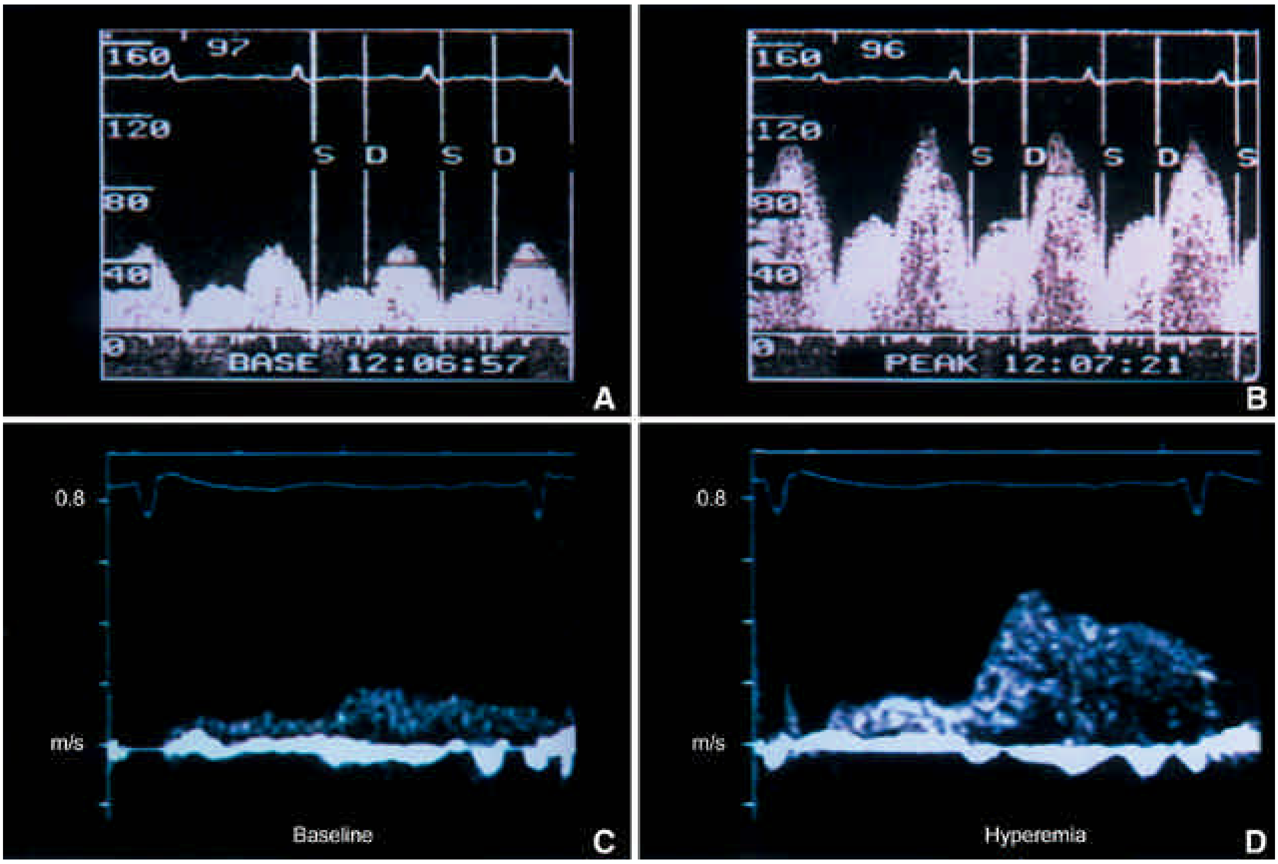

Fig. 2. An example of baseline and hyperemic flow velocity obtained by intracoronary Doppler wire method **(A, B)** and transthoracic echocardiography **(C, D)**.

Table 2. Coronary flow velocity measured by transthoracic and intracoronary Doppler study

No.	Age (year)	Sex	PDV (cm/s)				DSVR				CFR	
			TTDE		ICDW		TTDE		ICDW		TTDE	ICDW
			Baseline	Hyperemia	Baseline	Hyperemia	Baseline	Hyperemia	Baseline	Hyperemia		
1	28	m	22	75	20	62	-	-	2.0	2.5	3.9	3.2
2	62	m	13	38	22	60	3.2	2.0	2.2	2.4	3.4	2.7
3	70	f	23	70	40	70	1.6	1.4	2.0	1.7	2.9	2.0
4	46	m	16	42	45	110	-	-	2.0	1.8	3.3	2.8
5	51	f	22	69	46	93	1.9	1.5	1.8	1.5	3.2	2.4
6	67	f	26	44	33	60	-	-	2.8	2.5	1.8	1.9
7	58	f	23	80	30	80	3.1	1.7	2.0	1.5	3.3	2.9
8	58	f	20	67	60	125	2.1	1.5	1.6	1.4	3.3	2.2
9	61	f	27	92	57	120	2.4	1.8	2.1	1.5	3.2	2.8
10	45	f	24	67	50	100	2.5	2.0	2.3	1.5	3.0	2.7
11	58	f	29	76	75	130	-	-	2.8	2.2	2.2	2.0
12	48	f	34	90	55	100	3.2	2.5	2.7	1.8	2.7	2.0
13	54	f	17	51	63	130	2.7	2.5	2.7	1.7	3.1	3.0
14	62	f	27	86	52	110	1.5	1.2	2.8	1.7	3.0	2.4
15	51	m	21	58	60	110	1.7	1.5	2.2	1.4	3.2	2.5
16	43	m	13	50	32	70	2.7	1.6	2.1	1.7	4.0	2.8
17	68	m	19	53	40	115	2.4	1.6	2.0	1.9	2.7	2.7
Mean			22	65*,†	46	97*	2.4	1.7	2.2	1.8	3.1†	2.5
SD			5.6	17	15	25	0.6	0.6	0.4	0.4	0.5	0.4

TTDE, transthoracic Doppler echocardiography; ICDW, intracoronary Doppler wire; PDV, peak diastolic velocity; DSVR, diastolic and systolic velocity ratio; CFR, cornary flow reserve
*$p<0.05$ as compared to baseline, †$p<0.05$ as compared to intracoronary study

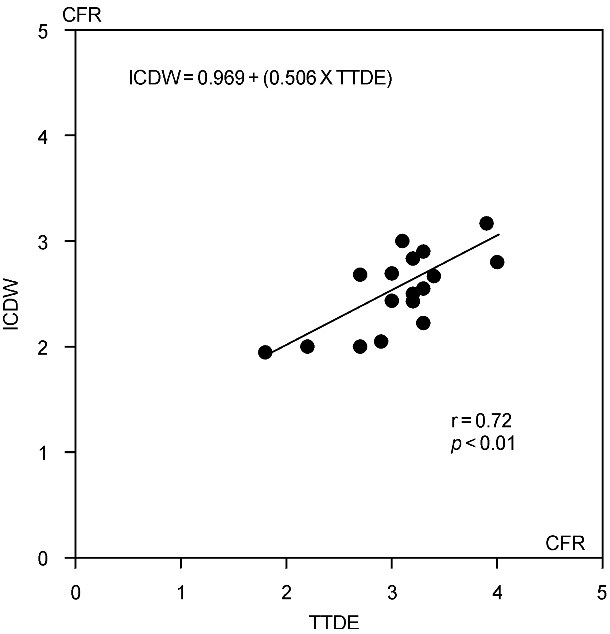

Fig. 3. Linear regression analysis between transthoracic and intracoronary Doppler measurement of coronary flow reserve (CFR). TTDE, transthoracic Doppler echocardiography; ICDW, intracoronary Doppler wire.

velocity ratio after hyperemia were similarly observed in both methods. CFR value obtained by TTDE was higher than the value calculated by ICDW method. There was a significant correlation between the values obtained by the two methods ($r=0.72$, $p<0.01$, Fig. 3).

DISCUSSION

In this study, we demonstrated that the transthoracic Doppler echocardiography is a feasible method in detecting distal coronary flow velocity in a majority of patient with patent LAD. The results of CFR by transthoracic Doppler echocardiography significantly correlated with those of Doppler wire method.

CFR provides a valulable information on the functional significance of epicardial coronary stenosis and microcirculatory function. The physiological significance of coronary lesions of intermediate severity is often difficult to determine from angiography alone (6, 7, 22). Coronary lesions of intermediate severity may have a differential CFR, thus CFR measurement allows a better definition of the functional importance of known coronary stenosis. Even angiographically normal coronary artery may shown early signs of atherosclerosis with reduced CFR (23). Syndrome X is a typical example of impaired CFR with patent coronary artery(8).

Measuring coronary flow velocity by intracoronary Doppler wire method is regarded as a gold standard. But its clinical utility is limited because of invasiveness. As a noninvasive method, positron emission tomography and transesophageal echocardiography can be used to measure CFR (24, 25). However, these methods are also limited to wide application due to expenses and semi-invasiveness. Recent advances in ultrasonic technology allows totally noninvasive coronary flow velocity measurement in distal LAD (20, 21). In the present study, measuring diastolic flow velocity was possible in 81% and measuring systolic flow velocity was possible in 67%. These results are comparable to previous studies (15-19). As the population of this study was limited to patent LAD, however, the detection rate for coronary flow velocity may be lower in patients with stenotic LAD. In that case, microbubble injection may increase the test result as a recent study indicated (26).

Coronary flow velocity measured by transthoracic Doppler echocardiography was lower than that measured by intracoronary Doppler wire method in present study both at baseline and hyperemic condition. This can be explained by several reasons. One is the incident angle between Doppler beam and course of LAD, resulting in underestimating the coronary flow velocity by transthoracic Doppler echocardiography. But the coronary flow velocity value and characteristics of the coronary flow patterns in this study agree well with previous studies (15-19). Another possibility is the different site of coronary flow measurement. Coronary flow velocity was measured at the mid left anterior descending artery with an intracoronary Doppler wire and at the distal portion with transthoracic Doppler echocardiography. Since the coronary flow velocity diminishes at the more distal portion (27), the smaller flow velocity at the distal portion is understandable. However, the diminishing patterns of diastolic to systolic coronary flow velocity ratio after vasodilator application was similar in both tests and flow patterns of higher coronary flow velocity during diastole than systole were identical in same patient by the two methods. Therefore, comparing coronary flow reserve rather than flow velocity may be more a reasonable and reliable way to exclude bias.

The CFR by transthoracic Doppler echocardiography was higher than those obtained by the intracoronary Doppler wire method. It may be expained partly by method in calculating coronary flow reserve between TTDE and ICDW. The systolic flow velocity could not be recorded in one third of cases by transthoracic Doppler echocardiography, thus the mean diastolic coronary flow velocity was used to calculate CFR. Meanwhile the CFR by intracoronary Doppler wire was automatically calculated by using an average of systolic and diastolic peak velocities. Because the incremental degree of systolic or diastolic coronary flow velocity by vasodilator is different between individuals, these factor may explains the different values in CFR between both tests.

The correlation between TTDE and ICDW in Hozumi et al.'s study was higher than our study (26). But their study was done at the same time, same vasodilator dose and administration route. The difference in baseline blood pressure between the two tests in our study may explains the lower correlation compare to their study. As the higher blood pressure causes higher coronary flow velocity, higher baseline pressure during intracoronary Doppler wire method caused lower CFR in same patient. During hyperemic condition, intravenous adenosine increased heart rate and decreased blood pressure significantly. These hemodynamic change after adenosine infusion may influence on coronary flow velocity.

It has been known that increases in heart rate augment resting coronary blood flow without altering maximal hyperemic flow (reducing the peak/resting velocity ratio), whereas increases in arterial blood pressure cause proportionately equal increases in resting and hyperemic blood flow (preserving the peak/resting velocity ratio) (28, 30). In our study, only hyperemic heart rate was higher during intravenous adenosine without baseline difference, so increment of heart rate during TTDE may not alter CFR value. Meanwhile, baseline and hyperemic blood pressure during TTDE was lower than intracoronary study significantly. The changes in mean blood pressure is the one of the influencing factor in altering coronary flow velocity. Thus, these difference in hemodynamic changes may influence the coronary blood velocity in multifactorial interrelated way.

The other difference with previous study is that we did not administer nitroglycerin before measuring coronary flow velocity by intracoronary Doppler wire method. As the nitroglycerin produces epicardial coronary vasodilation, the discrepancy of coronary flow velocity from previous study may explained partly by this factor (28). This may influence on lowering CFR measured by ICDW. This study differ in terms of vasodilator administration method and study population from previous study (20, 26, 29). But, there were significant correlations between the values obtained by the two methods ($r=0.72$, $p<0.01$) in present study and this could broaden clinical utility of TTDE determination of CFR in the evaluation of coronary circulation. Moreover, due to the virtue of this noninvasive test, it has the potential to be used as a follow up method or screening test for coronary microcirculatory function and an index of early sign of atherosclerosis.

There are several limitations in this study. First, the method to induce hyperemia and the test time were different in both tests. If we used the same vasodilator application method at the same time, the correlation of both tests may be higher. Secondly, recording the systolic coronary flow velocity was impossible in 33% of the cases. Because the incremental degree of systolic or diastolic coronary flow velocity by vasodilator is different between individuals, systolic coronary flow is needed in the calculation of the coronary flow reserve. Also further study to increase the detection rate of coronary flow velocity should be performed.

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