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Coronary Flow Velocity Immediately After Primary Coronary Stenting as a Predictor of Ventricular Wall Motion Recovery in Acute Myocardial Infarction

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OBJECTIVES The purpose of this study was to examine the relationship between the pattern of coronary blood flow velocity immediately after successful primary stenting and the recovery of left ventricular (LV) wall motion in patients with acute myocardial infarction (AMI).

BACKGROUND It is difficult to predict the recovery of LV wall motion immediately after direct angioplasty in AMI. Recent reports indicate that dysfunctional coronary microcirculation is an important determinant of prognosis for AMI patients after successful reperfusion.

METHODS We measured left anterior descending coronary flow velocity variables using a Doppler guide wire immediately after successful primary stenting in 31 patients with their first anterior AMI. The patients were divided into two groups: those with and those without early systolic reverse flow (ESRF). Changes in LV regional wall motion (RWM) and ejection fraction (EF) at admission and at discharge were compared between the two groups. Coronary flow velocity variables immediately after primary stenting were compared with changes in left ventriculographic indexes.

RESULTS The change in RWM was significantly greater in the non-ESRF group than it was in the ESRF group (0.9 ± 0.7 vs. −0.1 ± 0.3 standard deviation/chord, respectively, $p < 0.001$). The change in EF was also significantly greater in the non-ESRF group than it was in the ESRF group (10 ± 10 vs. 1 ± 6%, respectively, $p < 0.05$). In the non-ESRF group (diastolic to systolic velocity ratio [DSVR] <3.0), the DSVR correlated positively with the change in RWM ($r = 0.60$, $p < 0.005$, $n = 24$) and the change in EF ($r = 0.52$, $p < 0.01$).

CONCLUSIONS The coronary flow velocity pattern measured immediately after successful primary stenting is predictive of the recovery of regional and global LV function in patients with AMI. (J Am Coll Cardiol 2000;35:1835–41) © 2000 by the American College of Cardiology

The clinical effects of reperfusion have been confirmed using interventional therapies for acute myocardial infarction (AMI) (1,2). However, in our clinical practice, we have often encountered patients who, having undergone successful direct percutaneous transluminal coronary angioplasty, had variable recovery of left ventricular (LV) function.

Routinely, the physiologic significance of revascularization has been inferred from visual estimates of the percent residual stenosis (3,4), but the reliability of such estimates is limited by substantial interpretation variability (5–7). One contrast echocardiographic study demonstrated an absence of myocardial reflow even after successful recanalization (8). Moreover, progressive decreases in cardiac vein flow, suggestive of no reflow phenomenon, were observed in patients who underwent successful recanalization (9). These results illustrate that visual estimates derived from angiography have limitations for inference of the efficacy of successful recanalization and that the angiographic assessment of coronary patency does not necessarily reflect optimal myocardial reperfusion.

The recently developed intracoronary Doppler guide wire facilitates the measurement of the coronary flow velocity distal to coronary lesions immediately after direct angioplasty. Measurement of distal flow velocity after reperfusion might provide characterization of reflow. We presumed that the prognosis of the infarct region could be predicted by the observation of coronary flow velocity patterns after reperfusion. The objective of this study was to examine the relationship between the distal coronary flow dynamics of

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Abbreviations and Acronyms

ANCOVA	=	analysis of covariance
AMI	=	acute myocardial infarction
CPK	=	creatine phosphokinase
DSVR	=	diastolic to systolic velocity ratio of coronary flow
EF	=	ejection fraction
ESRF	=	early systolic reverse flow
LAD	=	left anterior descending coronary artery
LV	=	left ventricle
RWM	=	regional wall motion
SD	=	standard deviation
TIMI	=	Thrombolysis in Myocardial Infarction

culprit vessels immediately after successful primary stenting and the recovery of LV wall motion in patients with AMI.

METHODS

Patients. Between October 1997 and August 1998, 40 consecutive patients underwent successful primary coronary stenting in the proximal portion of the left anterior descending coronary artery (LAD) after they were diagnosed with their first anterior AMI, followed by LAD flow measurement by Doppler guide wire. The diagnosis of AMI was based on chest pain that was ≥30 min in duration, ST segment elevation of ≥2 mm in at least two electrocardiographic leads and Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 or 1 at the initial coronary angiography. They also had satisfactory dilation of culprit lesions as evaluated angiographically at the time of discharge. Nine patients were excluded from analysis because of inadequate image quality of Doppler signal. The remaining 31 patients (21 men and 10 women) were enrolled in this study. Written informed consent was obtained from each subject.

Angioplasty and stenting procedure. Direct coronary angioplasty was performed according to the clinical protocol at our institution. All patients were pretreated with heparin (100 IU/kg) and lidocaine (50 mg). Vascular access was obtained using the Judkins technique. The area of stenosis or obstruction in the LAD was crossed with an angioplasty guide wire in all patients, which was exchanged for a Doppler guide wire through the balloon catheter before the balloon was inflated. Dilation was performed with an appropriately sized balloon catheter. All 31 patients registered in this study underwent adjunctive coronary stenting. Palmaz-Schatz stents were deployed at nominal pressures with normal delivery systems, and all were then expanded with a noncompliant balloon of the same diameter as the reference vessel segment, with inflations in the range of 15 to 18 atm for 30 to 60 s. Dilations were concluded when the residual stenosis was equivalent to a <30% reduction in the diameter of the stenosis by visual assessment.

Coronary flow velocity measurements. All flow measurements before and immediately after successful primary coronary stenting were made with a Doppler-tipped angioplasty guide wire (FloWire, Cardiometrics, Mountain View, California). This Doppler guide wire is a 175-cm, 0.014-in. (0.036 cm), flexible, steerable guide wire with a 15-MHz transducer at its tip. Spectral analysis of the Doppler signal is performed, and velocity variables are calculated and displayed.

A Doppler guide wire was advanced across the culprit lesion and placed at least 3 to 4 cm distal to the lesion in the LAD. The position of the tip of the guide wire was confirmed by angiography. Coronary flow velocity was continuously measured until 20 min after the end of stenting. All recordings were made with the angioplasty balloon catheter retracted back into the guide catheter. The time-averaged value for each of the peak velocity, diastolic peak velocity, systolic peak velocity and diastolic to systolic velocity ratio (DSVR) (time-averaged diastolic peak velocity divided by time-averaged systolic peak velocity) were calculated and displayed on a Doppler velocimeter (FloMap, Cardiometrics, Mountain View, California) console. Twenty minutes after successful primary stenting, velocity recordings were made and brought into analysis.

Angiographic data analysis. Multiple orthogonal coronary views were obtained. A view that depicted the lesion in its narrowest dimension was selected for quantitative analysis. The angiographic percent stenosis was calculated by an automated edge detection method using the CCIP-310 (Catex Co. Ltd., Tokyo, Japan) system. These analyses were performed by two independent physicians. The percent stenosis was defined as the mean value of data from their measurements. Angiographic slow flow was defined as substantial flow reduction in the absence of critical residual stenosis, apparent thrombosis or distal vessel cut-off suggestive of embolization (10). This was decided by two angiographers who had no knowledge of the flow velocity data. Interobserver variability of measurements of angiographic percent stenosis (2.0% to 6.9%) was calculated as the difference in two measurements of the same patient by two different observers divided by the mean value.

Left ventriculogram analysis. Left ventriculograms were obtained in the 30° right anterior oblique projection with contrast medium utilizing a 9-in. (22.86 cm) image intensifier and a 30-frame/s filming rate. Dyes were injected using a mechanical injector with a total volume of 40 ml and an injection rate of 11 ml/s. The analysis was performed using the CCIP-310 (Catex Co. Ltd., Tokyo, Japan) system. The LV ejection fraction (EF; %) was evaluated by the area-length method and the regional wall motion (RWM; standard deviation [SD]/chord) by the centerline method (11). The EF and RWM evaluated by left ventriculography on admission (30 min after primary stenting) and at discharge (16 ± 2 [15–18] days later) were compared between the two groups. All measurements were performed

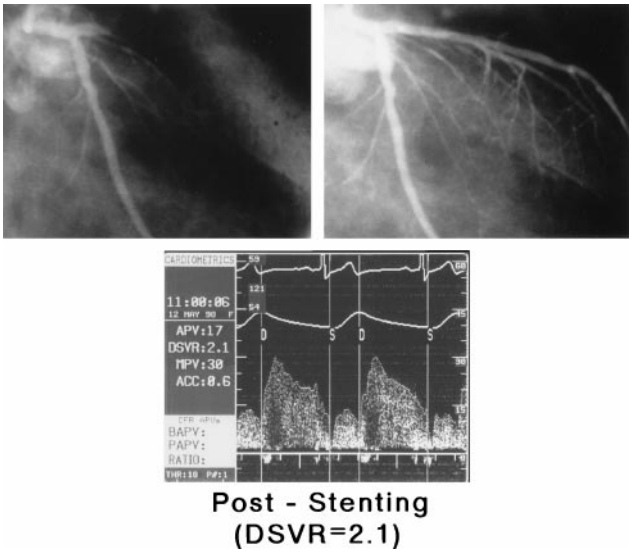

Figure 1. Coronary flow velocity configuration immediately after successful primary coronary stenting in a representative patient (a 64-year-old man) with normal DSVR and without early systolic reverse flow. This patient had an obstructed lesion at the proximal left anterior descending coronary artery, was treated with direct coronary angioplasty and stenting and showed satisfactory dilation of the offending lesion angiographically during the acute phase **(top panels)**. His coronary flow velocity pattern **(bottom panel)** improved distinctly after angioplasty and stenting (DSVR = 2.1). ACC = maximum acceleration of the instantaneous peak velocity; APV = averaged peak velocity; BAPV = baseline APV; DSVR = diastolic to systolic velocity ratio of coronary flow; MPV = maximum peak velocity; PAPV = hyperemic (peak) APV.

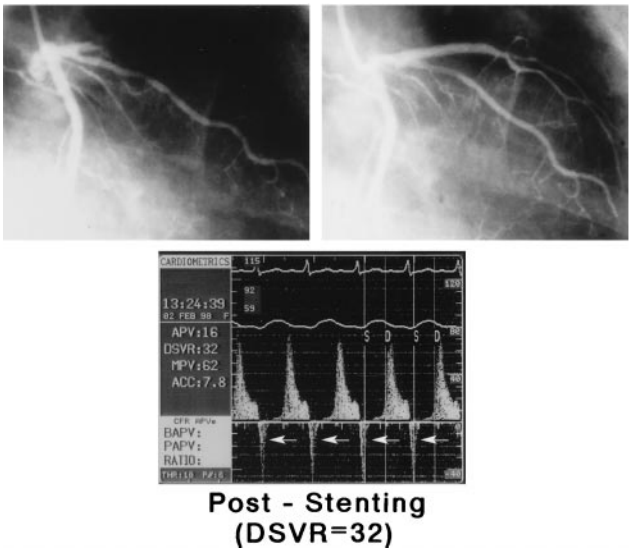

Figure 2. Coronary flow velocity configuration in a representative patient (a 55-year-old man) with ESRF and an extremely high DSVR immediately after successful primary coronary stenting. An obstructed lesion is present at the same site in the left anterior descending coronary artery as in Figure 1 **(top panels)**. He was also treated with primary coronary stenting and showed satisfactory dilation of the culprit lesion angiographically in the acute phase. However, his coronary flow velocity pattern **(bottom panel)** distinctly differed from that seen in Figure 1. He had almost no systolic antegrade flow, ESRF **(arrows)** and an extremely high DSVR (= 32). DSVR = diastolic to systolic velocity ratio of coronary flow; ESRF = early systolic reverse flow.

by two physicians who were blinded to the Doppler flow velocity data. The EF and RWM value were defined as the mean value of data from their measurements. Interobserver variability of measurements of EF was 2.5% to 8.6%, and that of RWM was 1.8% to 7.6%.

Statistics. All results are expressed as the mean value ±SD. The RWM and EF on admission and those at discharge were compared using a paired Student *t* test. An unpaired Student *t* test was used to compare the change in RWM and EF between groups. To gain insight into the influence of creatine phosphokinase (CPK), elapsed time from the onset of symptoms until reperfusion, or averaged peak velocity of LAD reflow on change in RWM or change in EF, we performed analysis of covariance (ANCOVA) using peak CPK, elapsed time or averaged peak velocity as covariates. Simple linear regression was performed to examine the relation between coronary flow velocity variables and change in RWM or change in EF. For all analyses, a p value <0.05 was considered significant.

RESULTS

Postangioplasty phasic velocity profiles. Representative examples of the immediately poststenting phasic velocity profiles in the LAD are shown in Figures 1 and 2. There were significant differences between these two patients in the coronary flow velocity patterns. Figure 1 shows the coronary flow velocity pattern in a patient with diastolic and systolic antegrade flow and a normal DSVR. By contrast, Figure 2 shows that this patient had almost no systolic antegrade flow, characteristic early systolic reverse flow (ESRF) and an extremely high DSVR. In this study, ESRF is defined as rapid reverse flow with peak velocity ≥10 cm/s and duration ≥60 ms (12). The ESRF was observed in 7 (23%) of the 31 patients. These patients were classified as the ESRF group (DSVRs; 5.9 to 32). The other 24 patients without ESRF were classified as the non-ESRF group.

Baseline characteristics. There were no significant differences between the two groups with regard to age, sex, peak CPK, history of preceding angina, Rentrop grade and percent diameter stenosis. The blood pressure and heart rate were similar in the two groups. However, patients in the ESRF group had a more prolonged elapsed time from the onset of symptoms until reperfusion. TIMI grade 2 reflow was observed in 4 of these 7 patients after stenting, and the other 3 patients demonstrated TIMI grade 3 reflow, whereas all 24 patients in the non-ESRF group had TIMI grade 3 reflow. Of the coronary flow velocity variables immediately after primary stenting, the averaged systolic peak velocity ($p < 0.0001$) and the DSVR ($p < 0.0001$) were significantly different between the two groups (Table 1).

Table 1. Baseline Characteristics of the ESRF and non-ESRF Groups

	ESRF (n = 7)	Non-ESRF (n = 24)	p Value
Mean age (yr)	66 ± 10	61 ± 8	NS
Men (%)	5 (71)	16 (67)	NS
Mean aortic pressure (mm Hg)	108 ± 36	116 ± 33	NS
Heart rate (beats/min)	91 ± 13	83 ± 12	NS
Single vessel disease–number (%)	4 (57)	14 (58)	NS
Elapsed time* (h)	9.6 ± 2.4	5.8 ± 2.3	< 0.001
Peak CPK (IU)	6,071 ± 1,678	4,371 ± 2,085	NS
Rentrop grade (0 or 1)–number (%)	7 (100)	16 (67)	NS
Antecedent angina–number (%)	3 (43)	10 (42)	NS
Percent diameter stenosis (%)			
on admission (immediately after angioplasty)	11 ± 9	8 ± 10	NS
at discharge	14 ± 9	13 ± 11	NS
Flow velocity variables			
APV (cm/s)	17.1 ± 6.4	18.8 ± 4.0	NS
ADPV (cm/s)	26.0 ± 9.9	22.7 ± 5.8	NS
ASPV (cm/s)	2.6 ± 1.4	13.1 ± 3.7	< 0.0001
DSVR	13.8 ± 10.5	1.8 ± 0.5	< 0.0001
			[mean ± SD]

*From symptom onset until reperfusion; †ADPV = averaged diastolic peak velocity.
APV = averaged peak velocity; ASPV = averaged systolic peak velocity; CPK = creatine phosphokinase; DSVR = diastolic to systolic velocity ratio; ESRF = early systolic reverse flow; NS = not significant; SD = standard deviation.

RWM by left ventriculogram. Figure 3 shows the changes in RWM for each group. The average RWM of the infarct area on admission was −2.5 ± 0.9 SD/chord in the ESRF group and −2.7 ± 0.9 SD/chord in the non-ESRF group (not significant). However, the RWM in the non-ESRF group was significantly better at discharge than on admission, while in the ESRF group it showed no significant improvement. The change in RWM was significantly greater in the non-ESRF group than it was in the ESRF group (0.9 ± 0.7 vs. −0.1 ± 0.3 SD/chord, $p < 0.001$). When ANCOVA was performed using peak CPK, elapsed time, or averaged peak velocity as covariates, the difference in change in RWM remained significant ($p < 0.005$, respectively).

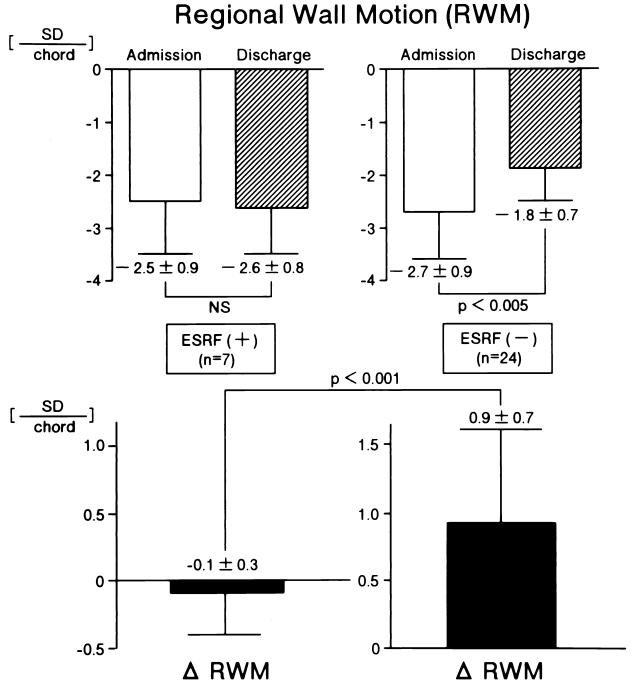

Figure 3. The change in RWM between discharge and admission. The Δ RWM is significantly larger in the non-ESRF group than it is in the ESRF group. ESRF = early systolic reverse flow; RWM = regional wall motion; SD = standard deviation.

EF by left ventriculogram. The EF on admission in the ESRF group (48 ± 11%) was not significantly different from that in the non-ESRF group (54 ± 9%). The EF at the time of discharge in the non-ESRF group was improved significantly, while that in the ESRF group showed no significant improvement. The change in EF in the ESRF group was 1 ± 6%, while that in the non-ESRF group was 10 ± 10% ($p < 0.05$) (Fig. 4). When ANCOVA was performed using peak CPK, elapsed time, or averaged peak velocity as covariates, the differences in change in EF remained significant ($p < 0.05$, respectively).

Correlations between coronary flow velocity variables and RWM or EF. A very poor recovery of RWM and EF can be predicted by ESRF alone in this study. We analyzed correlations between coronary flow velocity variables and the change in RWM or the change in EF in order to seek a new predictor for a recovery of LV function in the 24 patients without ESRF. The change in RWM and the change in EF did not correlate significantly with absolute variables (aver-

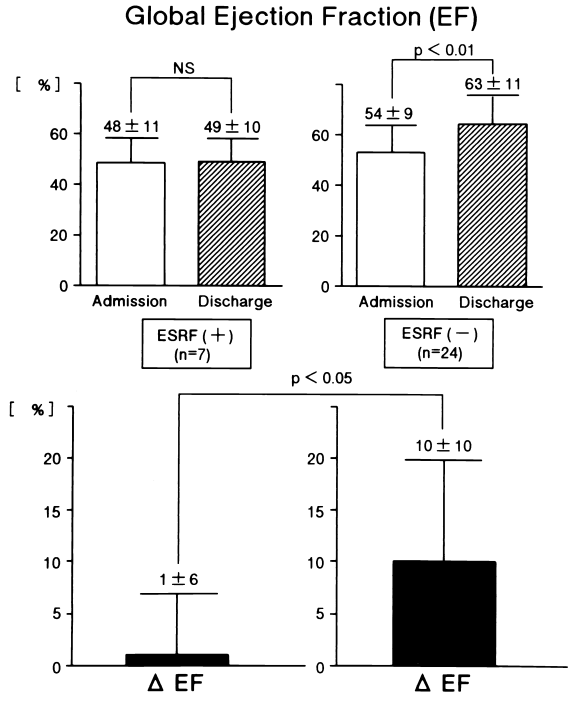

Figure 4. The change in EF between discharge and admission. The Δ EF is significantly larger in the non-ESRF group than it is in the ESRF group. EF = ejection fraction; ESRF = early systolic reverse flow.

aged peak velocity, averaged diastolic peak velocity and averaged systolic peak velocity) of coronary flow velocity immediately after primary stenting for the LAD. However, the DSVR correlated positively with the change in RWM ($r = 0.60$, $p < 0.005$, $n = 24$) and the change in EF ($r = 0.52$, $p < 0.01$) in the range of DSVR values <3.0 (Fig. 5). Thus, the correlation for RWM was stronger than that for EF. The patients in the ESRF group were excluded from this analysis. In these seven patients, almost no systolic antegrade flow (time-averaged systolic peak velocity <5.0 cm/s) was seen with ESRF. The DSVRs (5.9 to 32) in these patients were deemed unreliable due to the systolic flow velocity configurations.

DISCUSSION

Previous studies demonstrated normalization of distal flow velocity variables after relief of endoluminal obstruction (13,14). In contrast, in our relatively homogeneous group of patients who underwent successful primary stenting, the phasic coronary flow varied strikingly from patient to patient. The change in RWM and the change in EF in the ESRF group were apparently less than those in the non-ESRF group. This suggests that the coronary flow pattern immediately after primary stenting could be a predictor of recovery of LV function during the convalescent phase of AMI.

We did not find any flow velocity variables other than DSVR that correlated significantly with the change in RWM or with the change in EF. Several factors have been proposed as determinants of the absolute blood flow values in the infarct area, including collateral circulation (15), severity of stenosis (16), viscosity of blood, flow reserve capacity (17), preload and afterload (18) and the extent of the reperfusion injury and of "no reflow" phenomenon (19,20). Therefore, it is difficult to evaluate the microvascular flow to the myocardium from the absolute values of the coronary flow velocity alone.

Previous animal studies have revealed that, after reperfusion, infarcted myocardium contains some areas that have no reflow of blood (19,21). Ito et al. (8) reported that myocardial contrast echocardiography can be used to demonstrate a lack of myocardial perfusion immediately after successful recanalization. Specifically, myocardial contrast echocardiography established that the coronary microcirculation may be irreversibly damaged despite successful recanalization. These authors also reported that the residual contrast defect in the risk area present immediately after reflow (the no reflow phenomenon) is a predictor of poor functional recovery of the postischemic myocardium. Al-

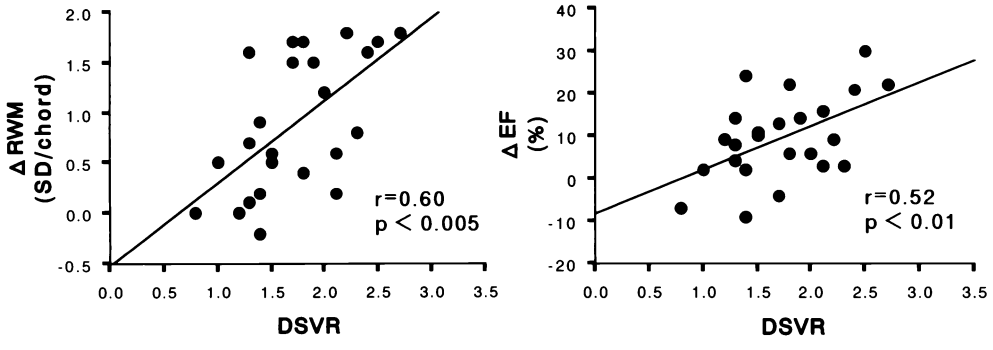

Figure 5. Correlation between DSVR and the changes in RWM and EF for the patients with infarcts in the left anterior descending coronary artery territory. The DSVR correlated positively with the Δ RWM **(left panel)** and with the Δ EF **(right panel)** in the range of DSVR values <3.0. This correlation for RWM is stronger than that for EF. DSVR = diastolic to systolic velocity ratio of coronary flow; EF = ejection fraction; RWM = regional wall motion.

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though the mechanism responsible for this phenomenon is not clear (22–24), this finding has been associated with extensive myocardial necrosis and microcirculatory damage. Our data may provide additional information from the point of view of coronary flow velocity. Our previous study (25) showed that phasic flow through a coronary artery with minimal residual stenosis after direct angioplasty may reflect microcirculatory injury, and we hypothesized that the observed flow change would predict recovery of LV function. Our data may indicate that ESRF is a parameter predicting poor functional recovery of LV wall motion. In our recent study using a canine model of AMI (26), we noted that the coronary flow velocity patterns immediately after reperfusion reflected pathologic characteristics of myocardium. Those findings appear to be consistent with the clinical data shown in this study.

Potential mechanism of reflow with a low DSVR or an ESRF. Epicardial phasic flow might be influenced by capacitive effects, epicardial critical stenosis (14,27), vasomotor tone, distending pressure (28) and extravascular pressure (28). Several potential mechanisms that could lead to a reduced phasic flow pattern are possible. In this study, we measured flow velocity variables in the LAD after successful primary stenting. Therefore, the contribution of residual epicardial stenosis not appreciated by angiography may be less influential. Reflow patterns with low DSVR may be explained by increased microvascular resistance and decreased extravascular pressure in the infarcted myocardium. Decreased extravascular pressure of the infarcted myocardium during systole might increase the apparent systolic flow, and increased vascular resistance might decrease the diastolic antegrade flow, which could result in a decrease of DSVR in mildly to moderately damaged myocardium. Therefore, we strongly suspect that the variability of the phasic flow pattern depends on the extent of microcirculatory damage and the systolic functional myocyte damage.

The seven patients with ESRF demonstrated markedly decreased late-diastolic flow and almost no systolic antegrade flow, which could result in an extremely high DSVR. Iwakura et al. (12) have reported that this reperfused coronary flow pattern was associated with TIMI grade 2 reflow and no reflow, as assessed by myocardial contrast echocardiography. They hypothesized that this flow pattern might result from an increase in microvascular impedance and a decrease in pooling blood volume in the myocardium. In our recent animal study (26), we also reported that coagulation necrosis and marked vacuolar degeneration of the myocardium may be related to the ESRF. They may compress the microvascular structures, and microvascular resistance may increase markedly during a cardiac cycle, especially during systole. The pooled blood in the myocardium during diastole cannot be transported into the coronary venous system during systole and is pushed back into the epicardial coronary arteries. Thus, an extremely high DSVR and occurrence of ESRF may predict very poor reperfusion after successful primary stenting.

Study limitations. Previous investigations (29–31) have demonstrated a correlation between coronary flow reserve and the severity of coronary stenosis or myocardial viability. The results of previous studies (32,33) suggest that coronary flow reserve may not become normalized immediately after angioplasty and that impairment of coronary flow reserve cannot be predicted by LV function. Although coronary flow reserve measurement was not performed in this study, it might be useful for detecting nonuniform distribution of myocardial infarction. Evaluations of coronary flow velocity pattern and flow reserve might lead to better understanding of the recovery of LV wall motion.

The DSVR measured within a few minutes after reperfusion may reflect a hyperemic reaction after direct angioplasty, and such hyperemia may indicate viable myocardium. In this study, we examined the DSVR value 20 min after reperfusion to obtain a standardized value. Short-term measurements, however, may not fully characterize postangioplasty reflow. Our previous study (34) demonstrated the safety of the Doppler guide wire for continuous monitoring of coronary flow in patients with AMI. We also reported that alterations in coronary flow velocity in recanalized infarcted arteries are related to the recovery of LV function in patients with successful direct balloon angioplasty (35). Classification by the pattern of time-course of the DSVR may more closely reflect the recovery of coronary flow and more accurately predict the recovery of LV wall motion. The correlation of clinical outcome with alterations in the configuration of flow velocity pattern is under investigation.

When systolic reverse flow was calculated as a negative value, DSVRs in the ESRF group would be negative numbers because of ESRF and almost no systolic antegrade flow. The number of negative DSVR cases is small in this study. The correlation of negative DSVR value with recovery of LV function is also under investigation.

The study population in this study was limited to patients with anterior AMI undergoing LAD stenting. Examinations in other coronary arteries may be necessary to provide more clinical relevance of this study.

Clinical implications. Recent reports have emphasized that TIMI grade 2 flow after reperfusion is not indicative of therapeutic reperfusion. Our findings suggest that the reflow patterns in patients with ESRF may imply extensive damage to the microcirculation even after successful dilation of arterial lesion. Therefore, this flow pattern might be one of the predictors for estimating the recovery of ventricular function in AMI. This flow pattern may also suggest the necessity for intraaortic balloon pump support, in view of its beneficial effects on the outcome in patients with this reflow pattern after primary coronary stenting. It may also be true that such patients might derive benefit from the addition of a thrombolytic agent, prolonged heparin, intravenous nitro-

glycerine, a calcium channel blocker or more than one of these.

Conclusions. Measurements of coronary flow velocity immediately after reperfusion may provide additional insight into the management of patients with AMI. Coronary flow velocity patterns immediately after primary stenting may be useful for predicting the recovery of regional and global LV function in patients with AMI.

Acknowledgments

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