Relation of Phasic Coronary Flow Velocity Characteristics With TIMI Perfusion Grade and Myocardial Recovery After Primary Percutaneous Transluminal Coronary Angioplasty and Rescue Stenting

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Background—A residual stenosis and/or microvascular damage have been proposed as mechanisms of TIMI 2 flow for acute myocardial infarction. Coronary flow dynamics were assessed in patients with TIMI 2 flow to predict whether additional intervention would improve TIMI grade.

Methods and Results—In 35 patients who had a successfully recanalized anterior acute myocardial infarction using angioplasty or rescue stenting, coronary flow patterns were compared with corresponding TIMI grade and regional left ventricular wall motion (LVWM) 1 month after the intervention. After angioplasty, the time-averaged peak velocity (APV) was lower in patients with TIMI 2 flow (n=22) than in those with TIMI 3 flow (n=13; 7.9±3.9 versus 20.6±5.1 cm/s; P<0.001). Two different flow patterns were recorded in patients with TIMI 2 flow (versus TIMI 3, P<0.001); patients with type 1 TIMI 2 flow (n=15) had a reduced diastolic APV (8.3±4.8 versus 24.2±7.4 cm/s), prolonged diastolic deceleration time (1176±455 versus 728±205 ms), and a small diastolic/systolic APV ratio (1.3±0.6 versus 2.1±0.7); patients with type 2 TIMI 2 flow (n=7) had systolic flow reversal (systolic APV, −7.9±4.6 versus 11.7±4.5 cm/s), a rapid diastolic deceleration time (221±84 versus 728±205 ms), and a negative diastolic/systolic APV ratio (−2.1±1.4 versus 2.1±0.7). A significantly lower mean chord LVWM (−3.0±0.2 versus −1.9±0.8; P<0.001) and a greater number of chords <−2SD (50±2 versus 28±18; P<0.001) were present in patients with type 2 versus type 1 TIMI 2 flow. Stenting increased TIMI 2 flow to TIMI 3 flow more in patients with type 1 than type 2 flow (67% versus 0%; P=0.003). Patients with TIMI 2 flow after stenting continued to demonstrate a type 2 pattern, and they had poor LVWM recovery.

Conclusions—The differentiation between 2 types of TIMI 2 flow can predict the improvement of TIMI grade and LVWM recovery after additional stenting. (Circulation. 2000;101:2361-2367.)

Key Words: angioplasty ■ coronary disease ■ diagnosis ■ myocardial infarction ■ reperfusion

The Thrombolysis in Myocardial Infarction (TIMI) Study Group grading scale1 has been widely accepted as a semiquantitative measure of coronary perfusion. Some have reported that the outcome of patients with TIMI 2 flow does not differ from that of patients with reperfusion failure.2 Recently, however, early TIMI 2 flow was associated with left ventricular (LV) functional recovery if flow normalized at follow-up.3 TIMI 2 flow may be due to a smaller minimal lumen diameter and a higher incidence of incomplete clot lysis and thrombus in the infarcted vessel.4 Although percutaneous transluminal coronary angioplasty (PTCA) produces superior recanalization rates and improved clinical outcomes when compared with thrombolytic therapy,5–6 persistently slow flow may indicate microvascular dysfunction associated with poor LV functional recovery.7–9 The differentiation between a residual stenosis and/or microvascular dysfunction as the main cause of slow radio-contrast flow in the infarct-related artery has implications for therapy and LV functional recovery.

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Characteristic coronary flow velocity patterns with suppressed diastolic velocity and a smaller diastolic/systolic flow velocity ratio have been demonstrated in the poststenotic region.10–11 In patients with an acute myocardial infarction (AMI), slow-flow velocity has been reported in patients who have TIMI 2 flow12 with a characteristic coronary flow velocity pattern (systolic retrograde flow and rapid deceleration of diastolic flow) that is associated with the “no-reflow” phenomenon (determined using myocardial contrast echocardiography).13 Because 2 different types of coronary flow...
velocity patterns may be expected in TIMI 2 cases, we hypothesized that the type of flow velocity pattern in the infarcted artery could differentiate a residual coronary stenosis from microvascular damage. The purpose of this study was to assess the coronary flow dynamics of TIMI 2 flow before and after intervention for AMI to predict whether additional coronary intervention would improve TIMI grade and LV recovery.

Methods

Study Patients
The study population consisted of 35 consecutive patients who had a successfully recanalized anterior AMI using primary PTCA (with or without rescue stenting) within 6 hours after the onset of symptoms. The diagnosis of AMI was defined as (1) chest pain continuing for >30 minutes, (2) ST elevation >2.0 mm in ≥2 contiguous precordial ECG leads, (3) an increase of serum creatine phosphokinase >3-fold of normal value, and (4) TIMI grade 0, 1, or 2 flow at initial coronary angiography. Patients with previous myocardial infarction, valvular heart disease, primary myocardial disease, and cardiogenic shock were excluded from the study. After written informed consent was obtained, emergency coronary angiography, PTCA (with or without rescue stenting), and coronary flow velocity recordings were performed as previously described.10–13

Coronary Angiography
Coronary angiography was performed using the standard femoral approach. All patients received an intravenous injection of 4000 U of heparin and an intracoronary injection of 2 mg of isosorbide dinitrate before angiography. Cinefilm was recorded at a speed of 30 frames/s. The angiographic TIMI flow grade of the infarcted left anterior descending coronary artery (LAD) was assessed before and after interventions using a cine projector with a frame counter, as previously described.12,14 Angiographic collateral circulation was assessed before PTCA in accordance with the report of Rentrop et al.15 To measure the percent diameter stenosis of the culprit lesion of the LAD, quantitative coronary angiography was performed using an auto-edge detection method with a commercially available system (CMS, Medical Imaging Systems), according to the previous report.16–17 An 8-Fr guiding catheter (Cyber, Scimed, Boston Scientific) was used as a reference. Follow-up coronary angiography and left ventriculography were also performed in the same way using a 5-Fr catheter (Selecon, Clinical Supply) 1 month (21 ± 6 days) after intervention.

Coronary Intervention
After the diagnostic angiography, PTCA was performed in the usual manner with a standard 8-Fr guiding catheter, balloon catheters, and a 0.014-inch, 15 MHz, Doppler-tipped angioplasty guidewire (FloWire, Cardiometrics).18,19 This was done after the administration of additional heparin to maintain an active clotting time >300 s. No other anticoagulant or antiplatelet agents were administered. Angioplasty success was defined as <30% residual stenosis angiographically with TIMI 3 flow. In cases with ≥30% stenosis and/or TIMI 2 flow, rescue stenting was performed with a Palmaz-Schatz stent (Johnson & Johnson). The final end point of coronary intervention, with or without rescue stenting, was defined as a residual stenosis <30% (determined angiographically), with TIMI 2 or 3 flow. The balloon/artery ratio was obtained at the end of the intervention.

Coronary Flow Velocity Recordings
Coronary flow velocities were recorded in the mid-LAD, distal to the culprit lesion, using the Doppler guidewire and a velocimeter (FloMap, Cardiometrics) after coronary angiography and after the interventions that were done according to the previous reports.10–12,18,19 The time-average of the instantaneous spectral peak velocity (time-averaged peak velocity [APV]) during 1 cardiac cycle, the systolic and diastolic APVs, the diastolic/systolic APV ratio (DSVR), and the deceleration time of the diastolic velocity were measured from phasic coronary flow velocity recordings using off-line computerized planimetry in the same manner as previously reported.13 Coronary flow velocity reserve was obtained from the ratio of maximal hyperemic APV (induced by 0.14 mg · kg⁻¹ · min⁻¹ adenosine infusion intravenously) to the baseline resting APV.

Regional LV Function
LV wall motion (LVWM) was assessed by left ventriculograms obtained 1 month (21 ± 6 days) after intervention and analyzed by the centerline method.20–22 The mean value of each chord motion and the number of chords more severe than –2SD below the mean of a normal reference was obtained in the territory of the LAD defined by chords 10 to 66.20,22

Statistical Analysis
All data are expressed as mean ± SD. Unpaired t tests were performed to compare the angiographic data, hemodynamic characteristics, and coronary flow velocity data in the 2 groups of TIMI 2 flow after PTCA. One-way ANOVA was used to compare the 5 groups of TIMI 2 or 3 flow before and after PTCA and after stenting, and a Scheffe F-test was performed if the ANOVA showed significant differences. Incidences of flow improvement from TIMI 2 to 3 were compared with the χ² test. P < 0.05 was considered significant.

Results

Patient Subgroups and Clinical Data
Baseline clinical characteristics and hemodynamic data are shown in Table 1. At the initial coronary angiography, TIMI grades 0, 1, 2, and 3 were observed in 9, 10, 16, and 0 cases, respectively (Figure 1). After primary PTCA, TIMI 2 flow was observed in 22 cases, and TIMI 3 flow in 13, including 6 who achieved sufficient angiographic criteria. No cases had TIMI 0 or 1 flow.

Rescue stenting after PTCA was performed in all 22 patients with TIMI 2 flow because of incomplete results by angiography and/or TIMI grade and in 7 of the 13 patients with TIMI 3 flow because of an insufficient angiographic end point.

After rescue stenting, TIMI 2 flow was demonstrated in 12 cases and TIMI 3 flow was obtained in 17. Ten of 22 cases with TIMI 2 flow after PTCA improved to TIMI 3 flow after rescue stenting. Twelve patients remained in the TIMI 2 flow group, despite rescue stenting (Figure 1). TIMI 3 flow was obtained in 23 patients, including 17 with and 6 without a stent; TIMI 2 flow was observed in 12 patients after final intervention.

No significant differences existed in the clinical characteristics or hemodynamic data among the 5 groups of patients with TIMI 2 or TIMI 3 flow that are listed in Table 1.

Coronary Angiography Data
In the frames-to-opacification count of coronary angiography (Table 1), no significant differences existed among the 3 groups of patients with angiographic TIMI 2 flow before and after PTCA and after stent implantation (P = 0.40). A significant difference was demonstrated between the groups with TIMI 2 and TIMI 3 flow (P < 0.001).

The percent diameter stenosis in patients with TIMI 2 flow before and after angioplasty was significantly greater than that in patients with TIMI 3 flow. No significant difference existed in the percent diameter stenosis between cases with TIMI 2 flow after stenting and those with TIMI 3 flow. The minimum lumen
Follow-up angiography demonstrated a patent LAD in all 35 patients. No significant differences in percent diameter stenosis existed among groups.

**Coronary Flow Velocity Data: Comparison Between TIMI 2 and TIMI 3 Flow**

Before angioplasty, a characteristic phasic flow velocity pattern with a reduced APV accompanying a restricted
diastolic APV, prolonged diastolic deceleration time, and a small DSVR (type 1 pattern, Figures 2 and 3) was observed in 15 of 16 patients with TIMI 2 flow; it was different from the TIMI 3 flow pattern (Figure 3).

After angioplasty, type 1 flow was observed in 15 of the 22 cases (Table 2 and Figure 1) with TIMI 2 flow. However, a different phasic flow pattern, with a restricted APV accompanying a systolic flow reversal, negative DSVR, and rapid diastolic deceleration was observed in the remaining 7 cases (type 2 pattern; Table 2 and Figures 2 and 3). As a result, each of the indices in cases with TIMI 2 flow after angioplasty had intermediate values resulting from the average of the 2 different flow patterns (Table 3). Figure 4 shows changes in APV, systolic APV, DSVR, and deceleration time during the 3 study periods.

After stenting, a type 2 flow pattern was demonstrated in all patients with TIMI 2 flow (Table 3 and Figure 4). No significant differences existed in coronary flow velocity patterns in TIMI 3 flow patients after PTCA or stenting (Table 3). In 7 of 13 cases with TIMI 3 flow after angioplasty, no

| TABLE 2. Phasic Coronary Flow Velocity Patterns and Regional LVWM in Patients With TIMI 2 Flow After PTCA |
|------------------------|------------------------|------------------------|
|                       | Type 1 (n=15)         | Type 2 (n=7)          |
| Coronary flow velocity |
| APV, cm/s             | 8.9±4.2*              | 5.7±1.9*              | 0.178    |
| Baseline              | 16.2±7.1*             | 10.3±5.0*             | 0.216    |
| Hyperemia             | 1.4±0.3               | 1.2±0.2               | 0.583    |
| CFVR                  | 13.0±6.0              | –16.4±8.2*            | <0.001   |
| SPV, cm/s             | 11.4±5.2*             | 26.9±8.6              | <0.001   |
| DPV, cm/s             | 8.7±4.5               | –7.9±4.6*             | <0.001   |
| SAPV, cm/s            | 8.3±4.8*              | 11.0±5.7*             | 0.260    |
| DAPV, cm/s            | 1.3±0.6*              | –2.1±1.4*             | <0.001   |
| DSVR                  | 1176±455*             | 221±84*               | <0.001   |
| DcT, ms               | Mean chord motion, SD/chord | –1.9±0.8              | –3.0±0.2* | <0.001 |
| LV wall motion at 1-month follow-up | No. of chords <−2SD | 28±18                  | 50±2*    | <0.001 |

CFVR indicates coronary flow velocity reserve; DAPV, diastolic time-averaged peak velocity; DcT, deceleration time of diastolic velocity; DPV, diastolic peak velocity; SAPV, systolic time-averaged peak velocity; and SPV, systolic peak velocity. *P<0.001 vs TIMI 3 flow.
significant differences existed in coronary flow indices before and after stenting. Furthermore, among the 3 types of patients with TIMI 3 flow, including the 6 patients who achieved angiographic criteria without stenting, 7 who underwent additional stenting because of angiographic criteria, and 10 who improved from TIMI 2 to 3 flow after rescue stenting (Figure 1), no significant differences existed in the indices of coronary flow.

Phasic Coronary Flow and Relation to LV Function Recovery
LVWM 1 month after treatment showed that mean chord motion was significantly smaller and the number of chords $< -2SD$ of LVWM was significantly greater in patients with TIMI 2 flow after stenting compared with those with TIMI 3 flow. No significant differences existed in mean chord motion and number of chords $< -2SD$ of LVWM among patients with TIMI 2 flow both before and after angioplasty and those with TIMI 3 flow (Table 1). In cases with TIMI 2 flow after angioplasty, mean chord LVWM was significantly smaller and the number of chords $< -2SD$ of LVWM were significantly greater in type 2 compared with type 1 patients (Table 2). Furthermore, among the 3 different groups with TIMI 3 flow including 6 cases without stenting, 7 cases who were in TIMI 3 before and after stenting, and 10 cases who obtained TIMI 3 after stenting (Figure 3), no significant differences existed in mean chord motion and number

Discussion
The present study demonstrated that coronary flow velocity measurements can distinguish between 2 different types of phasic TIMI 2 flow patterns after AMI recanalization and that these flow patterns are associated with different degrees of improvement in TIMI grade and LV function. Patients with the type 1 pattern (reduced APV with depressed diastolic APV, prolonged diastolic deceleration, and small DSVR) had a greater achievement of TIMI 3 flow, with good LVWM recovery after additional stenting. Patients with type 2 flow (restricted APV with systolic flow reversal and rapid diastolic deceleration) remained at TIMI 2, with poor LVWM recovery even after stent implantation. Thus, these 2 types of TIMI 2 flow predicted whether rescue stent implantation would improve outcome after PTCA for AMI, despite an angiographically successful PTCA result.

TIMI 2 Flow Before Angioplasty and After Stent Implantation
A restricted APV, indicating a small amount of antegrade coronary flow (confirmed by greater TIMI frame count compared with TIMI 3 flow), was observed in patients with TIMI 2 flow, which is consistent with earlier studies. This reduced APV in the infarcted LAD was seen in cases both before PTCA and after stenting; the difference is attributable to the degree of stenosis in the infarcted coronary artery. Depressed diastolic APV and a small DSVR in the distal coronary artery have been reported in cases with a significant coronary stenosis. In these cases, a restricted APV may also be expected, without coronary stenosis. In the present study, this characteristic flow pattern was demonstrated in patients with TIMI 2 flow before PTCA, which is consistent with the presence of a significant coronary stenosis. In cases with the no-reflow pattern caused by microvascular damage after angiographically successful reperfusion, a coronary flow velocity pattern with early systolic retrograde flow and rapid diastolic deceleration has been described. In these cases, a restricted APV may also be expected, without coronary stenosis. In the present study, this distinctive flow pattern was observed in 12 cases with TIMI 2 flow, even after stenting. Thus, in patients with TIMI 2 flow, the mechanism of slow antegrade flow may be different before angioplasty and after stenting, despite the similar angiographic TIMI grade. A significant coronary stenosis may cause type 1 TIMI 2 flow, and microvascular damage, type 2 TIMI 2 flow. As a result, flow velocity patterns, as shown in this study, can differentiate these 2 mechanisms.

TIMI 2 Flow After Balloon Angioplasty
Seven patients with type 2 flow after PTCA had a similar type 2 TIMI 2 flow after rescue stenting. The mechanism of the phasic flow pattern in these 7 cases is thought to be related to microvascular damage; this is supported in part by the fact that the flow velocity pattern did not change after the elimination of the stenosis by stent implantation. In addition,
poor LVWM recovery was also demonstrated in these TIMI 2 patients after rescue stenting. It has been reported that the outcome of patients with TIMI 2 flow does not differ from that of patients with reperfusion failure,\(^2\) which is consistent with the current findings. These data imply that type 2 TIMI 2 flow after intervention may be caused predominantly by microvascular damage.

In the 15 type 1 cases with TIMI 2 flow after angioplasty, the coronary flow velocity pattern showed reduced APV with suppressed diastolic APV and a small DSVR, which is consistent with a residual coronary stenosis. The greater percent diameter stenosis in these cases compared with patients after stenting and those with TIMI 3 flow also supports the presence of residual coronary stenosis. In these type 1 cases, additional stenting was associated with an improvement of TIMI grade and LVWM recovery in 10 of the 15 patient. In cases with AMI, it is difficult to estimate the degree of coronary stenosis by angiography alone, especially after angioplasty due to thrombus in the culprit lesion. However, the Doppler flow velocity patterns may indicate a significant residual stenosis, despite an angiographically insignificant appearance.\(^2\)\(^3\)

The remaining 5 of the 15 type 1 cases demonstrated type 2 TIMI 2 flow after the release of the residual stenosis by additional stenting, which is consistent with persistent microvascular damage. This result suggests that, in cases with a significant epicardial coronary stenosis combined with microvascular dysfunction in AMI, the epicardial coronary stenosis may be the main limiting factor of the coronary flow pattern and that microvascular dysfunction might be concealed. Microvascular dysfunction can play an important role in coronary flow dynamics only after the release of the significant stenosis. Further study in patients with both coronary stenosis and microvascular damage would help to resolve the mechanism involved in the conversion from type 1 to type 2 flow patterns in patients with TIMI 2 flow.

From the practical point of view, the differentiation between TIMI 2 flow caused by microvascular damage and that by a residual stenosis is important because additional stenting in cases with microvascular damage without a stenosis would be unhelpful, whereas additional intervention would improve flow in cases with a residual stenosis.\(^3\) Furthermore, as shown here, better

### TABLE 3. Coronary Flow Velocity Data

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<th>TIMI 2 Flow</th>
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<th>After Stenting</th>
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Abbreviations as in Table 2.

\(^*P<0.001\) vs TIMI 3 after PTCA and TIMI 3 after stenting; \(†P<0.001\) vs TIMI 2 after stenting.

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**Figure 4.** APVs, systolic APVs (SPVs), diastolic deceleration times (DcT), and DSVR of patients with TIMI 2 and TIMI 3 flow before and after angioplasty (PTCA) and after stent implantation. ● indicates TIMI 2 flow, and ○ demonstrates TIMI 3 flow; △ indicates patients with TIMI 3 flow who obtained angiographic end point without stenting.
LVWM recovery could be expected, with flow improvement from TIMI 2 to TIMI 3.

Study Limitations

Several limitations of the present study must be considered. Although the degree of coronary artery stenosis was assessed by quantitative angiography in the present study, the limitations of angiography in determining the percent diameter stenosis after intervention are well known.23 Thrombus in the culprit lesion makes it more difficult to estimate the degree of stenosis correctly in the acute period. Also, the study patients were limited to those with anterior AMI. The predominance of systolic flow and small DSVR have been described in the right coronary artery.11,24,25 The differentiation between TIMI 2 flow with a significant coronary stenosis and TIMI 3 flow may be more difficult in the right coronary artery. Finally, the number of study patients is relatively limited. However, the study patients were consecutive. The clinical, angiographic, and coronary flow results of intervention were similar to previous studies.7,13 Relatively higher creative phosphokinase releases were observed in patients with TIMI 2 flow and, although not statistically different from that of patients with TIMI 3 flow, these levels may reflect larger infarcts and a greater chance for no reflow patterns.

Conclusions

Two different types of phasic coronary flow velocity patterns are associated with TIMI 2 flow. Type I flow has a reduced diastolic peak velocity, prolonged diastolic deceleration, and a small DSVR, suggesting a residual coronary stenosis. It is associated with improved flow and LV function after stenting. Type 2 flow has systolic flow reversal and rapid diastolic deceleration, indicating microvascular damage, and it does not usually improve after intervention. The differentiation between these 2 types of TIMI 2 flow using Doppler flow velocity measurements may facilitate decisions regarding additional lesion intervention for an AMI after angiographically successful PCTA.

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References


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