The Pattern of Alteration in Flow Velocity in the Recanalized Artery Is Related to Left Ventricular Recovery in Patients With Acute Infarction and Successful Direct Balloon Angioplasty

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Objectives. We evaluated the relationship between alterations in coronary flow velocity during the acute phase of acute myocardial infarction (AMI) and the recovery of left ventricular wall motion in patients who underwent successful primary angioplasty.

Background. The status of the coronary microcirculation is the major determinant of the prognosis of patients who have had successful reperfusion after AMI. Animal studies have shown that dynamic changes in regional flow are associated with the extent of infarction. Evaluation of alterations in coronary flow velocity in infarcted arteries may provide information about microcirculatory damage.

Methods. Flow velocity of the distal anterior descending artery was continuously monitored with the use of a Doppler guide wire immediately after recanalization for 18.64 h in 19 patients who underwent successful primary angioplasty after anterior AMI. Subjects were divided into two groups on the basis of the time course of alterations in average peak velocity (APV). Group D consisted of patients who had progressive decreases in APV through the next day (n = 9), and Group I comprised patients with an increase in APV after a transient decline (n = 10). Ejection fraction (EF) and regional wall motion (RWM) were assessed by left ventriculography performed on admission and at discharge.

Results. The APV at the end of monitoring was greater in group I than in group D. In group I, EF and RWM were significantly improved at discharge. The change in EF was greater in group I than in group D (17 ± 9% vs. 4 ± 9%, p = 0.007), as was the change in RWM (0.96 ± 0.23 vs. 0.13 ± 0.36 SD/chord, p < 0.0001).

Conclusions. The alteration in flow velocity in recanalized infarcted arteries is related to left ventricular recovery. A progressive decrease in velocity after angioplasty implies no reflow, which is associated with a poor recovery of left ventricular function. Reperfusion injury may account in part for this phenomenon.

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Reperfusion therapy is an established method of salvaging the infarcted myocardium of patients who have had an acute myocardial infarction (AMI) (1,2). However, recent studies have shown that successful reperfusion of an occluded epicardial coronary artery does not always lead to preservation of left ventricular function (3). Experiments in animals suggest that the no reflow phenomenon or reperfusion injury is the major reason that left ventricular function can not be salvaged, even after adequate recanalization (4–6). Reflow may be impaired for several hours after recanalization, a deleterious effect caused by progressive decreases in regional flow associated with microvascular occlusion in the myocardium (7,8). Other animal experiments have shown that microvascular damage might be reversible after coronary reflow (9–11).

Measurement of coronary vein flow has been used to evaluate serial changes in perfusion status in patients who have had AMI (12). No reflow (that is, absence of myocardial perfusion even after successful recanalization) has been demonstrated using contrast echocardiography (6,11,13). This method is hampered by procedural complexity and difficulties in continuous assessment.

The recently developed Doppler guide wire has been used to evaluate the severity of coronary stenosis or the state of microvascular perfusion. The instantaneous spectral peak velocity has been validated as an accurate correlate of absolute flow (14,15). Continuous flow velocity monitoring in the catheterization laboratory has been found to be safe and useful (16). Thus, we used this method to ascertain whether the
A catheter was withdrawn from the guiding catheter, leaving the confirmed by fluoroscopic guidance. After PTCA, the balloon than 4 cm distal to the lesion. The location of the wire tip was detail (17). In brief, a Doppler guide wire was placed more continuous flow velocity monitoring has been reported in this protocol.

The primary stent implantation was not performed in the clinical protocol used at our institution. Dilation with use of a conventional balloon was concluded when the residual stenosis was less than 30% of the diameter by quantitative analysis. The percent diameter stenosis and the minimum luminal diameter were determined. The development of collaterals were graded angiographically according to the Rentrop classification (18). Well-developed collaterals were defined as grade 2 or 3. Angiographic slow flow of the left anterior descending artery after angioplasty was defined as poor contrast run-off compared with that of the circumflex coronary artery, without angiographically apparent dissection or distal embolization (19–21). Angiograms were visually evaluated by two independent physicians who had no knowledge of the flow velocity data.

Methods

Patient population. We continuously monitored flow velocity of an infarcted artery after successful primary angioplasty was performed in 47 patients between March 1993 and February 1997. Six patients with inferior infarctions and two with posterolateral infarctions were not included in the study. Patients with previous infarction late recanalization (elapsed time >12 h), distal culprit lesion and suboptimal PTCA results were also excluded. The remaining 29 patients with a first anterior AMI who underwent early recanalization of the left anterior descending artery within 12 h of onset of chest pain were enrolled in this study. The diagnosis of AMI was based on the symptom of severe chest pain lasting more than 20 minutes, electrocardiographic findings corresponding to ST segment elevation over the chest leads and an increase of the creatine kinase level to more than twice the normal value. Moreover, 10 patients were excluded from the present study for the following reasons: spontaneous guide wire dislocation at the mid-stage of monitoring (two patients), monitoring duration less than 12 hours (two patients), spontaneously recanalized infarcted artery (four patients) and no follow-up angiography (two patients). Therefore, the final study population consisted of 19 patients. The average duration of continuous monitoring was 18 ± 4 h (range, 12 to 26 h). Written informed consent was obtained from each subject. The study protocol was approved by the committee on Clinical Research of Toho University Ohashi Hospital.

Direct angioplasty. After intracoronary administration of 2.5 mg of isosorbide dinitrate, multiple orthogonal coronary projections were obtained. We performed PTCA according to the clinical protocol used at our institution. Dilution with use of a conventional balloon was concluded when the residual stenosis was less than 30% of the diameter by quantitative analysis. The primary stent implantation was not performed in this protocol.

Monitoring of continuous flow velocity. The technique of continuous flow velocity monitoring has been reported in detail (17). In brief, a Doppler guide wire was placed more than 4 cm distal to the lesion. The location of the wire tip was confirmed by fluoroscopic guidance. After PTCA, the balloon catheter was withdrawn from the guiding catheter, leaving the guide wire in the coronary artery. The guiding catheter was dislodged from the left main ostium. The entire system was sutured and secured to the patient’s leg. Patients were then moved to the coronary care unit for observation. They remained at rest during monitoring.

The average peak velocity (APV) was automatically calculated with a fast Fourier transformation and displayed on a Doppler velocimeter (FloMap®, Cardiometrics, Mountain View, CA). Studies were recorded onto VHS videotape and prints were made at various times. The APV value was determined every 2 to 4 hours, beginning 15 minutes after PTCA and ending the next day. Systemic blood pressure and heart rate were also recorded serially. If an intraaortic balloon pump (IABP) was used, it was turned off for at least 5 minutes during the velocity measurement. No complications related to intracoronary guide wire placement occurred in this study.

Classification of APV time course alterations. The time course pattern was recognized from velocity plots at various times, determined arbitrarily. The patients were divided into two groups, on the basis of the pattern of flow velocity alteration assessed by advent point of minimum APV. Group D consisted of nine patients who showed progressive decreases in APV from 4 h after intervention to the end of monitoring. Therefore, the minimum APV of this group occurred at the end of continuous monitoring. Group I consisted of 10 patients who showed gradual increments of APV after a transient decrease 4 to 8 h after primary PTCA. In this group, the minimum APV value was found 4 to 8 h after PTCA (4 h in six patients, 6 h in one and 8 h in three). In 4 of 10 patients, the maximum APV value was at the end of continuous monitoring.

Angiographic data analysis. The severity of coronary narrowing was determined by angiography using an automated edge detection algorithm (CCIP-310, Cathexy, Tokyo, Japan) in multiple orthogonal views. The guiding catheter was used as a reference. The percent diameter stenosis and the minimum luminal diameter were determined. The development of collaterals were graded angiographically according to the Rentrop classification (18). Well-developed collaterals were defined as grade 2 or 3. Angiographic slow flow of the left anterior descending artery after angioplasty was defined as poor contrast run-off compared with that of the circumflex coronary artery, without angiographically apparent dissection or distal embolization (19–21). Angiograms were visually evaluated by two independent physicians who had no knowledge of the flow velocity data.

Medication protocol. All patients received a bolus intravenous injection of 10,000 U of heparin before intervention. The intravenous infusion of heparin was continued until the next day (10,000 U for 24 h). Additionally, trans-guiding catheter administration (100 U/h) of heparin was also continued during monitoring to prevent thrombus formation in the catheter. As an antiplatelet agent, aspirin (162 mg/day) was given orally alone. Angiotensin-converters enzyme inhibitors (2.5 to 5 mg of enalapril or 7.5 to 15 mg of delapril) were administered shortly after intervention and continued throughout the hospital stay. Calcium channel blocking agents or nitrates were

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<tr>
<td>APV</td>
<td>average peak velocity</td>
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<tr>
<td>EF</td>
<td>ejection fraction</td>
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<tr>
<td>IABP</td>
<td>intraaortic balloon pump</td>
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<tr>
<td>PTCA</td>
<td>percutaneous transluminal coronary angioplasty</td>
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<tr>
<td>RWM</td>
<td>regional wall motion</td>
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administered to some patients who had a hypertensive tendency during the acute stage of infarction. None of the subjects received beta blockers, catecholamines, other inotropic agents or drugs that exerted a cardioprotective action (such as verapamil, papaverine, or adenosine) (22-24).

**Evaluation of left ventricular function.** Left ventriculograms were obtained at a 30° right anterior oblique projection with contrast medium. The protocol called for a 9-in. image intensifier and a filming rate of 30 frames per second. The global left ventricular ejection fraction (EF) was evaluated by the area-length method and regional wall motion (RWM) by the center-line method.

Left ventriculography was performed on admission (before angioplasty) and at discharge (16 ± 6 days later). Both EF and RWM were compared between the groups. All measurements were performed by a physician who had no knowledge of the Doppler flow velocity data.

**Statistics.** Statistical analysis was performed using StatView 4.02 on a Macintosh Centris 650 computer. Continuously distributed variables were expressed as mean ± standard deviation. The unpaired t test was used to compare clinical determinants and velocity values; an F test was applied. Other variables were compared using the Mann-Whitney U test. The paired t test was used to evaluate serial changes in hemodynamics and angiographic variables. The pattern of the APV time course alteration in groups D and I was defined by two-way repeated analysis of variance. Categoric variables were compared by Fisher’s exact test. A level of p < 0.05 was considered statistically significant.

**Results**

**Clinical characteristics.** The study population consisted of 15 men and 4 women, with a mean age of 64 ± 9 years (range 50 to 79 years). The average elapsed time from AMI onset to recanalization was 4.5 ± 2.5 h. Antecedent angina, defined as some chest symptoms within the 24 h before the onset of infarction, was present in 11 patients.

Baseline clinical characteristics of the two groups are listed in Table 1. There were no differences between groups D and I in age, gender, history of antecedent angina, elapsed time from onset to recanalization or peak creatine kinase value. In group D, four patients belonged to Killip class 1 and five patients to Killip class 2; in group I, 9 of 10 patients belonged to Killip class 1. The frequency of IABP use was similar in both groups. The reason for IABP use was maintenance of patency after angioplasty. The counter pulsation assist was stopped within 24 hours after angioplasty on the day after angioplasty in all patients.

Angiographic characteristics in both groups are given in Table 2. There were no differences in baseline antegrade flow, the frequency of well-developed collaterals and the lesion location.

**Time course of alterations in flow velocity.** Data from APV monitoring in each patient are shown in Figure 1. The data showed a unique time course of alteration in velocity through-out monitoring. In all patients, the difference between maximum and minimum APV was more than 30%. Group D showed an average 56 ± 11% decrease in APV (range 39% to 67%) from maximum value (Fig. 1A), and lowest APV occurred at the end of monitoring. In group I, the APV was lowest within 4 to 8 h after PTCA (average 47 ± 10% decrease from baseline, range 30% to 57%) and then showed an average 95 ± 43% increase from its lowest point (range 41% to 193%) (Fig. 1B).

The APV values 15 minutes after PTCA and 4 h later were similar in both groups. However, group I had a higher APV at the end of monitoring than group D (21 ± 9 cm/sec vs. 9 ± 4 cm/sec, p = 0.002). The time course of alteration in APV values at these three points was markedly different in the two groups (p < 0.0001). (Fig. 2). Cyclical flow variation, as noted by Anderson et al. and Kern et al. (16,25), was not observed in any patients.

**Comparison of angiographic findings.** The lesion in each patient was in the proximal left anterior descending artery. Angiographic slow flow on the final angiogram was found in 6 (67%) patients in group D. In contrast, no slow flow was found in group I (Table 2). In all patients, good patency of the infarcted artery endured at discharge. In group D, the percent diameter stenosis of the culprit lesion before angioplasty, immediately after angioplasty and before discharge was 90.9 ± 10.9%, 22.1 ± 6.2% and 20.4 ± 5.1%, respectively. In group I, these values were 90.5 ± 10.3%, 23.7 ± 7.2% and 26.6 ± 5.1%, respectively. There were no differences between the groups.

**Hemodynamics.** Mean arterial pressure measurements 15 minutes after primary PTCA, 4 h later and at the end of monitoring were similar in both groups. No significant time course variances in hemodynamics were observed throughout the study between the groups. Similarly, the heart rate was not different between the groups. There was no difference in left ventricular end-diastolic pressure measured before the reperfusion procedure (Table 3).

**Recovery of left ventricular function.** The EF on admission was 48 ± 12% in group D and 46 ± 9% in group I (p = 0.67). The EF at discharge was 52 ± 14% in group D and 62 ± 8%
in group I \( (p = 0.071) \). The change in EF was significantly greater in group I than in group D \((17 \pm 9\% \text{ vs. } 4 \pm 9\%, \ p = 0.007)\) (Fig. 3A).

The RWM on admission was \( 2.3.00 \pm 0.31 \text{ SD/chord} \) in group D and \( -2.95 \pm 0.23 \text{ SD/chord} \) in group I \( (p = 0.75) \). The RWM at discharge was \( -2.87 \pm 0.46 \text{ SD/chord} \) in group D and \( -1.99 \pm 0.42 \text{ SD/chord} \) in group I \( (p = 0.0004) \). The change in RWM was significantly greater in group I than in group D \( (0.96 \pm 0.23 \text{ vs. } 0.13 \pm 0.36, \ p < 0.0001) \) (Fig. 3B). In three patients in group D, RWM was worse at discharge than on admission.

Discussion

Animal studies have demonstrated that microvascular occlusion can develop in the area at risk after reperfusion, resulting in a progressive decrease in regional flow \( (3,7,8,26) \). No reflow has been shown to develop and progress for several hours after recanalization \( (7,8,27) \). Thus, the evaluation of flow changes after restoration of an occluded infarcted artery could provide useful information about the effects of the reperfusion procedure on myocardial salvage in the clinical setting. We found that the pattern of alterations in flow velocity in the successfully recanalized artery was related to recovery of left ventricular function.

Left ventricular function in patients with AMI is determined by several factors, including the area at risk supplied by the infarcted artery, development of collateral flow \( (28,29) \), elapsed time after PTCA and the presence of antecedent angina \( (12,30,31) \). The number of electrocardiographic leads with ST segment elevation did not differ between groups. Additionally, the lesion location was similar in both groups. Thus, the extent of myocardium at risk appeared to be similar in both groups. Other clinical characteristics, including collateral grading and elapsed time, were not different in the two groups. It seems reasonable that the recovery of the infarct-related region of the left ventricle depends on the pattern of alteration in flow velocity after reperfusion in patients who have undergone successful primary PTCA.

Proposed mechanism of flow velocity alteration. Several factors could determine the blood flow in the region of infarction, including collateral circulation, severity of stenosis,

<table>
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<tr>
<th>Characteristic</th>
<th>Group D</th>
<th>Group I</th>
<th>p Value</th>
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<tr>
<td>TIMI 0</td>
<td>6</td>
<td>6</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>TIMI 1 + 2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Poorly developed</td>
<td>6</td>
<td>6</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Well developed</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lesion location proximal of major</td>
<td>56</td>
<td>50</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>septal branch (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angiographic slow flow after angioplasty (%)</td>
<td>67</td>
<td>0</td>
<td>0.003</td>
</tr>
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</table>

TIMI = Thrombolysis in myocardial infarction.
Table 3. Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group D</th>
<th>Group I</th>
<th>p Value</th>
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<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>15 min</td>
<td>98 ± 9</td>
<td>0.71</td>
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<tr>
<td></td>
<td>4 h</td>
<td>96 ± 8</td>
<td>0.92</td>
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<tr>
<td></td>
<td>Next day</td>
<td>97 ± 5</td>
<td>0.60</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>15 min</td>
<td>79 ± 13</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>77 ± 10</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>Next day</td>
<td>74 ± 10</td>
<td>0.07</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>Before angioplasty</td>
<td>23 ± 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Next day</td>
<td>21 ± 4</td>
<td>0.55</td>
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LVEDP = left ventricular end-diastolic pressure; Next day = at the end of monitoring.

blood viscosity, flow reserve capacity (32), preload and afterload and the extent of the reperfusion injury (33,34). Therefore, it is difficult to evaluate the microvascular flow to the infarcted myocardium from the APV of the restored infarcted artery alone. Heart rate and blood pressure were not significantly different between groups. We cannot exclude the possibility that vasomotion alteration at the target lesion occurred during monitoring. However, our preliminary study of patients who had serial coronary angiography immediately after angioplasty, at the end of monitoring, and before discharge showed no deterioration in the residual stenosis. Residual stenosis appeared to remain constant. Moreover, flow velocity accurately correlates with absolute flow (14,15). Thus, we conclude that the dynamic alterations in flow velocity observed in this study accounted for the changes in blood supply to the infarcted myocardium. Previous animal studies have shown that no reflow associated with microvascular occlusion may progress for several hours after reperfusion (7) and that the extent of perfusion 4 h later after reflow correlated well with left ventricular prognosis (8).

In other studies (12,35), progressive decreases in cardiac vein flow suggestive of the no reflow phenomenon were observed in patients with AMI who underwent successful recanalization. In group D the extent of APV reduction during monitoring was 56 ± 11% (range 39% to 67%). This finding is consistent with results of a previous study in which no reflow was related to a >30% decrease from baseline cardiac vein flow during 24 h of monitoring (12). Progressive decreases in APV might indicate severe deterioration in perfusion, most likely attributable to progression of the no reflow phenomenon that is based on development of reperfusion injury. Conversely, a gradual increase in flow velocity might be explained by amelioration of tissue perfusion status. Temporary and reversible causes of poor perfusion include microvascular occlusion by blood cell stasis (36), vessel compression with myocardial tissue swelling (37), hyperreactivity of vascular tonus (38) and prolonged spasms (22). Resolution of prolonged reactive hyperemia followed by restoration of occluded infarcted arteries might also contribute to the mechanisms of initial reduction of flow velocity, but this conclusion remains speculative.

Although coronary flow reserve measurement was not performed in the present study, it might be useful for detecting nonuniform distribution of myocardial infarction. Serial coronary flow reserve measurements might lead to better understanding of the alterations in flow velocity observed in this study.

**Study limitations.** Flow velocity is parallel to absolute volumetric flow only when the cross-sectional area in examined vessels remains constant. None of our subjects showed significant lesion renarrowing at discharge. However, we did not confirm the lumen area by intravascular ultrasound. Furthermore, we cannot exclude the possibility that vasomotion after angioplasty is related to flow alteration. Continuous intravenous infusion of nitrate and stent implantation could help to eliminate and minimize the alteration of vasomotion and help maintain vessel dilation.

Absolute coronary flow is also dependent on heart rate, afterload and contractility. Although those factors were constant in both groups, we could not monitor the left ventricular end-diastolic pressure serially, which would have altered flow in the area at risk.

From a technical point of view, cardiac vein flow measurements are limited by difficulty in stabilizing catheter position and by lack of specificity for detecting changes in coronary artery flow (39,40). It is difficult to monitor flow status continuously by myocardial contrast echocardiography to detect the no reflow phenomenon after reperfusion therapy. Continuous coronary flow velocity monitoring has major advantages in real-time evaluation of reflow status. No special equipment and skills are needed in emergency situations. The performance issue regarding monitoring is positioning the guide wire tip and guide catheter. These were important technical problems (41). The true damage in the infarcted myocardium might...
not have been examined completely because a stunned myocardium might not have been restored at discharge (42).

**Clinical implications.** Data obtained by monitoring flow velocity could be important for risk stratification of patients with AMI who have undergone primary PTCA. Deterioration in flow velocity during monitoring may be related to infarct expansion and left ventricular remodeling. Moreover, this study shows that evaluation of alterations in flow velocity after primary PTCA might provide insight into dynamic changes of reperfusion status.

Intraaortic balloon pumping could augment myocardial perfusion and result in myocardial salvage (43,44). Drugs such as verapamil (20,22) and adenosine (24,45) might modulate reperfusion injury. Flow velocity monitoring might make it possible to study the pharmacologic responsiveness of the resistance vessels of infarcted regions. Prolonged velocity monitoring after successful primary angioplasty demonstrated two different time patterns of change in flow velocity. Progressive decrease of average velocity in the late stage is associated with poor recovery of left ventricular function, which is hypothesized to be related to regional impaired perfusion. The method described here could become a useful predictor of reflow status in patients with AMI.

**References**


