Coronary Flow Velocity Pattern Immediately After Percutaneous Coronary Intervention as a Predictor of Complications and In-Hospital Survival After Acute Myocardial Infarction

Atsushi Yamamuro, MD; Takashi Akasaka, MD; Koichi Tamita, MD; Kenji Yamabe, MD; Minako Katayama, MD; Tsutomu Takagi, MD; Shigefumi Morioka, MD

Background—Recently, it was reported that the degree of microvascular injury and left ventricular functional recovery during the chronic period can be predicted after treatment of the infarct-related artery based on the coronary flow velocity (CFV) pattern assessed using a Doppler guidewire. The aim of this prospective study was to examine whether the CFV pattern may predict complications and in-hospital survival after acute myocardial infarction (AMI).

Methods and Results—The study population consisted of 169 consecutive patients with a first anterior AMI successfully treated with percutaneous coronary intervention (PCI). We examined the CFV pattern immediately after PCI using a Doppler guidewire. In accordance with previous findings, we defined severe microvascular injury as a diastolic deceleration time $\geq 600$ ms and the presence of systolic flow reversal. Patients were divided into two groups: those without severe microvascular injury ($n=118$; group 1) and those with severe microvascular injury ($n=51$; group 2). All of the patients who had cardiac rupture were in group 2. Congestive heart failure (CHF) was observed more frequently in group 2 than in group 1 (53% versus 8%, $P<0.001$). The in-hospital cardiac mortality rate was significantly higher in group 2 than in group 1 (18% versus 0%, $P<0.001$). Nine patients in group 2 died, 5 patients because of CHF and 4 patients because of cardiac rupture.

Conclusions—These findings suggest that the CFV pattern is an accurate predictor of the presence or absence of complications and of in-hospital survival after AMI. (Circulation. 2002;106:3051-3056.)

Key Words: myocardial infarction ■ prognosis ■ microcirculation ■ reperfusion ■ ultrasonics

The Western Washington Intracoronary Streptokinase Randomized Trial demonstrated that achieving arterial patency was the main factor in the prognostic benefit of thrombolytic agents after acute myocardial infarction (AMI). Since then, numerous trials have validated this open-artery hypothesis. However, the continuing problem is that myocardial tissue perfusion cannot be achieved in some patients despite recanalization of the infarct-related artery. The failure to achieve adequate tissue perfusion is referred to as the no-reflow phenomenon, which occurs as a result of microvascular damage or intramyocardial edema induced by ischemia. On angiograms, the no-reflow phenomenon is defined as substantial coronary antegrade flow reduction (less than Thrombolysis in Myocardial Infarction [TIMI] flow grade 3) without epicardial mechanical obstruction. Recent studies have shown that angiographic contrast velocity after successful percutaneous coronary intervention (PCI), as defined by the TIMI criteria, predicts poor left ventricular (LV) functional recovery and a higher risk of cardiac mortality. Although TIMI flow grading seems to segregate effective from ineffective flow, this analysis is only a qualitative measure that is subject to interoperator bias and interlaboratory variability. Furthermore, because angiographic contrast velocity alone is not sufficient to assess microvascular damage, refinements in the quantification of the degree of microvascular injury have led to improvements in the prognostic value of this measurement. Our recent studies have demonstrated that microvascular injury can be assessed more quantitatively from coronary flow velocity (CFV) patterns obtained with a Doppler guidewire. Although the relation between the CFV pattern and clinical outcome has not been described in detail, we hypothesized that, against this background, the CFV pattern may be a predictor of prognostic implications. To investigate this hypothesis, we prospectively compared the CFV patterns immediately after primary PCI, complications, and in-hospital survival in 169 consecutive patients with a reperfused anterior-wall AMI.

Methods

Study Population
Between January 1997 and October 2001, 236 consecutive patients who were admitted to the coronary care unit (CCU) of Kobe General Hospital were included in this study. The exclusion criteria were as follows: patients who died in the hospital, patients with cardiogenic shock, and patients who did not undergo successful PCI. The remaining 169 patients were divided into two groups: those with a first anterior AMI who were successfully treated with PCI ($n=100$; group 1) and those with a first anterior AMI who were treated with PCI but died before discharge ($n=69$; group 2). The demographic characteristics were not significantly different between the two groups. The primary PCI was performed using a combination of balloon angioplasty and stent implantation. The procedural success was defined as TIMI flow grade 3. The primary endpoint was in-hospital mortality.
Hospital for their first MI of the anterior wall were considered for the study population. The diagnosis of AMI was defined as (1) continuous chest pain lasting >30 minutes, (2) ST elevation >2.0 mm in ≥2 contiguous precordial ECG leads, and (3) an increase in serum creatine phosphokinase >3-fold the normal value. Sixty-seven patients were excluded from analysis because of transfer in a state of cardiac arrest attributable to AMI (5 patients), referral from another hospital attributable to cardiac rupture complicating AMI (4 patients), chronic terminal renal failure (5 patients), coronary stenosis >90% in another coronary artery (24 patients), culprit lesion in the left main trunk (17 patients), inadequate coronary interventions (7 patients), inadequate Doppler recordings (3 patients), or atrial fibrillation at the time of CFV determination (2 patients). Therefore, this study was based on the remaining 169 patients (124 males, 45 females; mean±SD age, 62±10 years). All patients underwent primary PCI (with or without rescue stenting) of the culprit lesion and achieved successful coronary reflow (≥50% residual stenosis angiographically with TIMI grade 2 or 3) within 24 hours after the onset of chest pain. Of 169 patients who underwent PCI, thrombolytic therapy was administered only to 3. The study protocol was approved by the Committee for the Protection of Human Subjects in Research at Kobe General Hospital.

**Study Protocol**

Coronary angiography was performed following 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. After the diagnostic angiography, PCI was performed in the usual manner with balloon catheters and a 0.014-inch, 15-MHz, Doppler-tipped angioplasty guidewire (FloWire, Guidant). This was performed after the administration of additional heparin to maintain the activated clotting time at ≥300 seconds. 12-lead ECGs were recorded during and after PCI. Additional ST-segment elevation (>2 mm) immediately after balloon inflation or stenting and in the absence of mechanical obstruction was defined as ST reelevation. Serum creatine kinase (CK) was measured serially every 3 hours after recanalization until the peak value was obtained. The LV ejection fraction was calculated as (Systolic peak velocity (cm/s; SPV) and deceleration time of diastolic velocity at time of CFV determination (2 patients). Therefore, this study was based on the remaining 169 patients (124 males, 45 females; mean±SD age, 62±10 years). All patients underwent primary PCI (with or without rescue stenting) of the culprit lesion and achieved successful coronary reflow (≥50% residual stenosis angiographically with TIMI grade 2 or 3) within 24 hours after the onset of chest pain. Of 169 patients who underwent PCI, thrombolytic therapy was administered only to 3. The study protocol was approved by the Committee for the Protection of Human Subjects in Research at Kobe General Hospital.

**Coronary Flow Velocity Recordings**

Coronary flow velocities were recorded in the mid-left anterior descending coronary artery, distal to the culprit lesion, using the Doppler guidewire and a velocimeter (FloMap, Cardiometrics) immediately after PCI and according to previously described methods. The systolic peak velocity (cm/s; SPV) and deceleration time of diastolic velocity at time of CFV determination (2 patients). Therefore, this study was based on the remaining 169 patients (124 males, 45 females; mean±SD age, 62±10 years). All patients underwent primary PCI (with or without rescue stenting) of the culprit lesion and achieved successful coronary reflow (≥50% residual stenosis angiographically with TIMI grade 2 or 3) within 24 hours after the onset of chest pain. Of 169 patients who underwent PCI, thrombolytic therapy was administered only to 3. The study protocol was approved by the Committee for the Protection of Human Subjects in Research at Kobe General Hospital.

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**In-Hospital Data Collection**

The patients were followed up for the occurrence of complications until hospital discharge. Data on clinically relevant in-hospital events (death from any cause and reintervention) were carefully collected in the study forms. Another investigator also reviewed data on these patients. The type and frequency of ventricular arrhythmia were evaluated by Holter monitoring on the day of the infarction, and ECGs were recorded continuously until at least 5 days after the infarction. Malignant arrhythmia (including reperfusion arrhythmia) was defined as ventricular tachycardia (a minimum of 3 consecutive beats of ventricular origin at a rate of >100 bpm), and patients were monitored for the development of ventricular fibrillation, all the time during hospitalization.6 Left ventricular heart failure was defined as the presence of clinical congestive heart failure (the presence of a third heart sound, Killip class ≥2, Forrester subset of 2 or 4, dyspnea, or evidence of pulmonary congestion on chest radiographs).6 Patients were evaluated for the occurrence of cardiac rupture as well as for the presence of pericardial effusion and LV thrombi by two observers using echocardiography, as previously described.22–24

**Statistical Analysis**

Continuous baseline and outcome variables are expressed as mean±SD; whereas discrete variables are given as absolute values, percentages, or both. Continuous variables were compared with Student’s two-tailed t test. For comparison of rates of discrete outcome variables, y2 test or Fisher’s exact test was used. The contribution of factors resulting in complications and in-hospital death was evaluated by multivariate regression analysis. The stepwise selection method was used with inclusion criteria of P<0.05 to identify the variables remaining as independent risk factors for complications and in-hospital death. The variables examined included age ≥70 years, sex, hypertension, hyperlipidemia, diabetes, smoking, culprit lesion, multivessel disease, rescue stenting, time from onset of symptoms and treatment ≥6 hours, serum peak CK levels ≥4000 IU/L, LV ejection fraction ≤50%, collateral flow (Rontrop grade ≤1), TIMI flow grade ≤2, and CFV pattern of severe microvascular injury. The odds ratio and relative risk with 95% confidence intervals were calculated. Data analyses were performed using SAS Release 8.1 for Windows (SAS Institute Inc, 1999 to 2000). P<0.05 was considered significant.

**Results**

**Patient Characteristics**

One hundred eighteen patients did not have severe microvascular injury (group 1), and 51 had severe microvascular injury (group 2) (Figure). Patients with a TIMI 2 flow after PCI were observed more frequently in group 2 than in group 1. Patients with ST reelevation were observed more frequently in group 2 than in group 1. Hemodynamics on day 1 after the infarction was significantly poorer in group 2 than in group 1. The LV ejection fraction was significantly lower in group 2 than in group 1. Peak CK levels were significantly higher in group 2 than in group 1 (Table 1).

**Complications and In-Hospital Prognosis**

Table 2 summarizes the in-hospital complications and cases of cardiac death in the two groups. We observed more cardiac complications in group 2 than in group 1. The period of hemodynamic subset II or greater was significantly longer in group 2 than in group 1. Patients in group 2 stayed in the CCU significantly longer compared with group 1. The in-hospital cardiac mortality rate was significantly higher in group 2 than in group 1. In the group of patients without severe microvascular injury, there was no case of in-hospital
death, whereas 9 patients in the group with severe microvascular injury died during hospitalization. 5 patients (10%) because of congestive heart failure and 4 patients (8%) because of cardiac rupture.

Multiple regression analysis showed that severe microvascular injury as assessed based on the CFV pattern and multivessel disease were significant determinants of congestive heart failure. Similarly, severe microvascular injury was a significant independent predictor of cardiac rupture. Moreover, severe microvascular injury was also a significant independent predictor of in-hospital cardiac death as well as age and multivessel disease (Table 3). The odds ratios for cardiac rupture and severe microvascular injury are not shown, because cardiac rupture or cardiac death did not complicate myocardial infarction in any of the patients without severe microvascular injury. Tables 1 and 3 clearly show that although patients developing severe microvascular injury after recanalization of the infarct-related artery frequently demonstrated TIMI flow grade 2 angiographic contrast velocity, the CFV pattern rather than TIMI flow grade was an independent predictor of complications of myocardial infarction and in-hospital death.

**TABLE 1. Baseline Clinical and Angiographic Characteristics of Patients**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=118)</th>
<th>Group 2 (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±10</td>
<td>63±10</td>
<td>0.402</td>
</tr>
<tr>
<td>Male (%)</td>
<td>85 (72)</td>
<td>38 (75)</td>
<td>0.740</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>61 (52)</td>
<td>26 (51)</td>
<td>0.932</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>48 (41)</td>
<td>27 (53)</td>
<td>0.141</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>70 (59)</td>
<td>33 (65)</td>
<td>0.510</td>
</tr>
<tr>
<td>Smoking</td>
<td>71 (60)</td>
<td>33 (65)</td>
<td>0.578</td>
</tr>
<tr>
<td>Segment 6 (%)</td>
<td>68 (58)</td>
<td>37 (73)</td>
<td>0.066</td>
</tr>
<tr>
<td>Collaterals (Rentrop grade 1) (%)</td>
<td>100 (85)</td>
<td>47 (92)</td>
<td>0.142</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>25 (21)</td>
<td>16 (31)</td>
<td>0.156</td>
</tr>
<tr>
<td>Ischemic time, min</td>
<td>385±326</td>
<td>340±204</td>
<td>0.363</td>
</tr>
</tbody>
</table>

**TABLE 2. In-Hospital Clinical Complications**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=118)</th>
<th>Group 2 (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-wave infarction (%)</td>
<td>83 (70)</td>
<td>51 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent AMI (%)</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>0.904</td>
</tr>
<tr>
<td>Malignant arrhythmia (%)</td>
<td>42 (36)</td>
<td>31 (61)</td>
<td>0.002</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>10 (8)</td>
<td>27 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Period of hemodynamic subset II or greater, days</td>
<td>0.6±0.9</td>
<td>5.6±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days in the CCU</td>
<td>4.9±2.5</td>
<td>12.7±18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular thrombus (%)</td>
<td>4 (3)</td>
<td>14 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pericardial effusion (%)</td>
<td>13 (11)</td>
<td>32 (63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac rupture (%)</td>
<td>0 (0)</td>
<td>11 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oozing rupture (%)</td>
<td>0 (0)</td>
<td>8 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VSP</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.127</td>
</tr>
<tr>
<td>Blow-out-type (%)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>0.030</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>0 (0%)</td>
<td>9 (18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PCWP indicates pulmonary capillary wedge pressure; LV, left ventricular. VSP indicates ventricular septal perforation.
injury and LV functional recovery during the chronic period could be predicted by evaluating the CFV pattern after treatment of the infarct-related artery.\textsuperscript{14,15,26} The findings of the present study revealed that AMI is often complicated by congestive heart failure when microvascular injury is severe and that severe microvascular injury is always present when cardiac rupture occurs after recanalization. Probably for this reason, in-hospital death could be predicted more accurately from the CFV pattern, which allows a more quantitative assessment of microvascular injury, than from the angiographic contrast velocity.

\textbf{Coronary Flow Velocity Pattern and Complications}

To determine the therapeutic strategy is important to be able to predict the severity and duration of left ventricular dysfunction during the early stage after an AMI. The hemodynamics on day 1 after the infarction were significantly poorer in the group of patients with marked microvascular injury. Those patients stayed in the CCU significantly longer. These findings suggest that severe microvascular injury as assessed based on the CFV pattern is associated with poor hemodynamics even after successful PCI, resulting in a prolonged hospitalization period in the CCU. There is a study in which microvascular injury was evaluated by myocardial contrast echocardiography to investigate complications in patients with AMI.\textsuperscript{6} The authors reported that marked microvascular injury was associated with an increased incidence of congestive heart failure, and that this disorder was protracted. They divided patients into two groups, the group with marked microvascular injury and the group with less marked microvascular injury, and found no significant difference in hemodynamic findings. The difference between their findings and ours may be attributable to the difference in measurement time points.

Pericardial effusion was frequently observed in patients with severe microvascular injury. The transmurality of MI probably contributes to the occurrence of pericarditis, because Q-wave MI subsequently developed in all patients with severe microvascular injury, whereas 30% of patients without severe microvascular injury manifested non-Q-wave infarction. Pericarditis was observed more frequently in patients with Q-wave MI than in those with non-Q-wave MI.\textsuperscript{6} In all patients with a cardiac rupture, the CFV pattern of severe microvascular injury was present, with 2 patients with blow-out type, 1 patient with ventricular septal perforation, and 8 patients with oozing rupture. The 3 patients with acute cardiac rupture, consisting of 2 with blow-out type and 1 with ventricular septal perforation, fell into a sudden cardiac shock, could not be subjected to emergency cardiac surgery, and died. Regarding the 8 patients with oozing rupture, all of them displayed hemodynamics and echocardiographic findings of cardiac tamponade. Bloody effusion could be aspirated by pericardial drainage in all patients with oozing rupture. Only 1 of the 8 patients with oozing rupture died despite successful pericardial drainage. The extensive and transmural myocardial damage in cases of severe microvascular injury may contribute to the occurrence of blow-out type, ventricular septal perforation, or oozing rupture.

\textbf{Microvascular Injury and Coronary Flow Velocity Pattern}

Myocardial contrast echocardiography was suggested to be the only method available for the assessment of microvascular integrity. In patients showing no-reflow phenomenon by myocardial contrast echocardiography, the CFV pattern, as assessed using a Doppler guidewire, is characterized by the appearance of systolic retrograde flow, diminished systolic antegrade flow, and rapid deceleration of diastolic flow.\textsuperscript{21} We have reported the association between CFV patterns and LV functional recovery.\textsuperscript{14,15} In addition, the present study showed an association between this particular flow pattern and a poorer prognosis in terms of adverse events, especially congestive heart failure, cardiac rupture, and cardiac death.

All of these adverse events are associated with more extensive and transmural myocardial infarction. In patients with severer larger transmural myocardial infarction, the microvasculature shows loss of its anatomic integrity,\textsuperscript{8,27} which may markedly affect the CFV pattern. There may be some patients in whom the CFV pattern has already been determined by the size of the myocardial infarct before reperfusion therapy. However, it was reported that reperfusion therapy resulted in insufficient coronary microcirculation attributable to reperfusion injury, such as oxygen-free radical injury,\textsuperscript{28,29} calcium overload, microvascular spasm,\textsuperscript{10} neutrophil plugging of the microvessels,\textsuperscript{10} and tissue edema\textsuperscript{2} or embolization of the coronary microvasculature attributable to disintegration of thrombi and the contents of the disintegrated atheroma in the lesion to distal parts of the coronary vasculature.\textsuperscript{31,32} In the present study, in 75% of the patients with severe microvascular injury, an ST-segment relevation was observed in the absence of epicardial mechanical obstruction immediately after PCI. Therefore, microvascular injury is not only determined by the size of the infarction associated with myocardial ischemia but also by reperfusion injury and intervention-induced release of the thrombi and the contents of the disintegrated atheroma. In the patients without ST segment relevation showing the coronary flow velocity pattern with severe microvascular injury, the microvasculature disorder caused by myocardial ischemia before reperfusion therapy may have been severe. Considering modern reperfusion therapy, patients with microvascular injury accompanied by

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
Variables & Odds Ratio & 95\% CI & \(\chi^2\) & \(P\) \\
\hline
Congestive heart failure & & & & \\
Microvascular injury & 10.98 & 4.43 to 27.20 & 26.78 & <0.001 \\
Multivessel disease & 3.76 & 1.44 to 9.82 & 7.28 & 0.007 \\
Cardiac rupture & & & & \\
Microvascular injury & \ldots & \ldots & 21.05 & <0.001 \\
Cardiac death & & & & \\
Microvascular injury & \ldots & \ldots & 12.81 & <0.001 \\
Multivessel disease & 13.51 & 1.21 to 151.4 & 5.70 & 0.017 \\
Age \(\geq 70\) & 11.36 & 1.00 to 128.5 & 4.84 & 0.028 \\
\hline
\end{tabular}
\caption{Independent Predictors of Complications and In-Hospital Death}
\end{table}
an ST-segment reelevation may require microvascular preservation.

Limitations of the Study
The study population represented only 73% of the patients treated for anterior wall AMI at our center during the study period. Many of the excluded patients had stenosis of another coronary artery (>90%) or a culprit lesion in the left main trunk. These complications themselves profoundly influence the occurrence of in-hospital deaths. Patients referred from another hospital because of cardiac rupture complicating AMI were also excluded because their CFV patterns had not been obtained. Second, only patients with first anterior AMI were enrolled in this study. Therefore, the prediction of clinical outcome by CFV has not been established in patients with inferior or posterior AMI. Third, the factors influencing CFV patterns should be considered. In patients with aortic valve stenosis with a significant pressure gradient or hypertrophic cardiomyopathy with marked myocardial hypertrophy, the CFV pattern shows systolic flow reversal.33,34 In the present study, none of the patients had the above disorders. However, patients with the above disorders should be excluded. In addition, cardiac arrhythmias may affect the CFV. Therefore, we excluded patients with a nonsinus rhythm. Finally, the high incidence of cardiac ruptures observed in this study was expected because many patients with single vessel disease and without previous cardiac disease were included.

Clinical Implications
In previous studies, we reported an association between phasic CFV patterns and improvement in LV function as a factor indicative of a good prognosis after AMI. The present study clarified the CFV pattern indicative of severe microvascular injury as an important predictor of various complications of AMI in many patients, namely, of a poor prognosis. Among these complications, congestive heart failure, cardiac rupture, and cardiac death were closely associated with more extensive and transmural myocardial infarction. These high-risk patients can be detected by Doppler flowmetry during an earlier stage of AMI. In the modern era of reperfusion therapy, Doppler flowmetry is expected to additionally improve the evaluation and outcome of myocardial infarction patients by moving past angiographic flow to microvascular preservation.

References


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