Angiographic Assessment of Reperfusion in Acute Myocardial Infarction by Myocardial Blush Grade

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Background—Angiographic successful reperfusion in acute myocardial infarction has been defined as TIMI 3 flow. However, TIMI 3 flow does not always result in effective myocardial reperfusion. Myocardial blush grade (MBG) is an angiographic measure of myocardial perfusion. We hypothesized that optimal angiographic reperfusion is defined by TIMI 3 flow and MBG 2 or 3.

Methods and Results—In 924 consecutive patients with TIMI 3 flow after angioplasty for acute myocardial infarction, we prospectively studied the value of MBG. End points were death, MACE, enzymatic infarct size, and residual left ventricular ejection fraction. Follow-up was 16±11 months. Of the 924 patients, 101 (11%) patients had MBG 0 or 1. Mortality was significantly higher in patients with MBG 0 or 1 compared with patients with MBG 2 or 3 (relative risk, 4.7; 95% CI, 2.3 to 9.5; P<0.001). The combined incidence of MACE was higher in patients with MBG 0 or 1 compared with patients with MBG 2 or 3 (relative risk, 1.8; 95% CI, 1.1 to 2.8; P=0.009). Enzymatic infarct size was larger (1437±2388 versus 809±1672, P=0.001) and left ventricular ejection fraction was lower (37.7±10.6 versus 43.8±11.1, P<0.001) in patients with MBG 0 or 1 compared with patients with MBG 2 or 3.

Conclusions—MBG is a strong angiographic predictor of mortality in patients with TIMI 3 flow after primary angioplasty. Enzymatic infarct size is larger and residual left ventricular ejection fraction is lower in patients with MBG 0 or 1 compared with MBG 2 or 3. Angiographic definition of successful reperfusion should include both TIMI 3 flow as well as MBG 2 or 3. (Circulation. 2003;107:2115-2119.)

Key Words: angioplasty • myocardial infarction • reperfusion

Reperfusion treatment in acute myocardial infarction aims at early and sustained reperfusion of the myocardium at risk.1 Nowadays, reperfusion therapy for acute myocardial infarction is considered to be angiographically successful when TIMI 3 flow is achieved in the infarct-related coronary artery.2-3 However, even when TIMI 3 flow is achieved, some patients have less optimal reperfusion at the myocardial tissue level, and several mechanisms have been suggested to be involved as, among others, no reflow4 and distal embolization.5-7 Therefore, other predictors related to epicardial reperfusion as well as myocardial reperfusion are necessary. We previously described the myocardial blush grade (MBG) after primary angioplasty as an important predictor of infarct size and survival.8 After this study, several other authors confirmed these findings with a similar method in patients treated with primary coronary angioplasty9 and with a somewhat different method for patients after thrombolytic treatment and confirmed that myocardial blush is an independent predictor for outcome in acute myocardial infarction patients treated with reperfusion therapy.10-13 However, all of these studies were retrospective analyses on coronary angiographic data gathered for other purposes. Therefore, we now prospectively studied the value of this simple and available parameter in a large cohort of primary angioplasty patients with a mean follow-up of 16±11 months. The aim of our study was to test the hypothesis that a definition of successful reperfusion should include TIMI 3 flow in the infarct-related coronary artery but also MBG 2 or 3 in the myocardial territory of the infarct-related coronary artery.

Methods

Patients
We performed a single-center follow-up study. The protocol was reviewed and approved by our Institutional Review Board. From September 1998 to September 2001, 924 consecutive patients with TIMI 3 flow and a residual lumen diameter <50% after primary coronary angioplasty were enrolled in this analysis. All patients received intravenous aspirin, heparin, and nitroglycerine. The use of other medication, including IIb-IIIa receptor antagonists, was at the discretion of the attending physician.

Clinical and Angiographic Variables
Baseline clinical characteristics and outcome data were collected in a case record form. TIMI flow and MBG was assessed visually on
the angiogram and made immediately after the primary coronary angioplasty procedure by the performing cardiologist, and all data were entered prospectively into a database. MBG has been defined previously as follows: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. When myocardial blush persisted ("staining"), this phenomenon suggested leakage of contrast medium into the extravascular space and was graded 0. No digital techniques were used. To allow blush grading, the length of the angiographic run needs to be adequate. To ensure this, our final angiographic run is long enough to see the venous phase of the contrast passage. These angiographic runs were made in identical views according to the infarct-related artery and thus assuring assessment in equal conditions. When the left coronary artery was involved, the final angiogram was made in the left lateral view. When the right coronary artery was involved, the final angiogram was made in the right oblique view. Reproducibility of the visual assessment of the MBG has been studied in our first report, and we found a good reproducibility and intraobserver and interobserver variabilities of 90% and 97%, respectively. For this study, a sample of 120 coronary angiograms was reviewed by an independent observer without access to clinical data or case record forms and patients were classified as MBG 0/1 or 2/3. In this sample, 17 patients had been classified by the operator in the category 0/1. The independent observer graded 3 additional patients as grade 0/1, and agreement existed in 117 of the 120 of patients (97%). Survival was independent observer graded 3 additional patients as grade 0/1, and, therefore, we studied patients with MBG 2 or 3 as one group and compared them with patients with MBG 0 or 1, as other authors have done.11,12,14–16 Other angiographic variables were infarct-related artery, TIMI flow before angioplasty, and multivessel coronary artery disease.

End Points

Primary end points were mortality and the combined incidence of death, nonfatal recurrent myocardial infarction, and new revascularization (MACE) at follow-up of at least 6 months. Secondary end points were infarct size as measured by enzymatic infarct size and left ventricular ejection fraction before discharge. Enzymatic infarct size was estimated by measurement of serial lactate dehydrogenase (LDH) activity. Cumulative enzyme release from 5 to 6 serial measurements up to 48 hours after symptom onset (LDH48) was calculated, as previously described.14 Patients were scheduled for predischarge left ventricular ejection fraction measurement. The multiple-gated equilibrium method was used after in vivo labeling of red cells with 99 m-Tc-pertechnetate. A gamma camera (General Electric) with a low-energy, all-purpose, parallel-hole collimator was used. The global ejection fraction was calculated automatically by a computer (Star View, General Electric) with the PAGE program, as described before in detail.17

Statistical Analysis

Statistical analysis was performed using SPSS 10.0. Differences between group means were tested by 2-tailed Student’s t test. A χ² statistic was calculated to test differences between proportions, with calculation of relative risks (RRs) and exact 95% CIs. The Fisher exact test was used when the expected value of cells was <5. Statistical significance was defined as P<0.05. Cumulative survival curves for the risk of mortality were constructed according to the Kaplan-Meier method, and differences between the curves were tested for significance by the log-rank statistic. Cox proportional-hazards regression models were used to estimate hazard ratios of angiographic variables.

Results

Follow-up was at least 6 months in all patients, and mean follow-up was 16±11 (range, 6 to 48) months. No patient was lost to follow-up. During the entire period, 38 patients died (mortality, 4.1%). Residual left ventricular ejection fraction was measured in 871 (94%) patients, and enzymatic infarct size was measured in 669 (80%) patients. Out of the 924 patients with TIMI 3 flow after angioplasty, 101 (11%) patients had MBG 0 or 1 and 823 (89%) patients had MBG 2 or 3. These 2 patient groups with TIMI 3 flow had somewhat different baseline variables. The patients with MBG 0 or 1

### Table 1. Clinical Variables of Patients With TIMI 3 Flow After Angioplasty for Acute Myocardial Infarction According to the MBG

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>MBG 0 and 1 (n=101)</th>
<th>MBG 2 and 3 (n=823)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±12</td>
<td>60±12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76 (75)</td>
<td>634 (77)</td>
<td>0.69</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
<td>69 (68)</td>
<td>391 (47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>17 (17)</td>
<td>83 (10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>29 (29)</td>
<td>236 (29)</td>
<td>0.99</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>9 (9)</td>
<td>84 (10)</td>
<td>0.19</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>37 (37)</td>
<td>423 (51)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>14 (14)</td>
<td>184 (22)</td>
<td>0.05</td>
</tr>
<tr>
<td>Referred patients (%)</td>
<td>50 (49)</td>
<td>341 (41)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ischemic time, min</td>
<td>260±192</td>
<td>234±140</td>
<td>0.12</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; Ischemic time, time from symptom onset to first balloon inflation.

### Table 2. Angiographic Variables of Patients With TIMI 3 Flow After Angioplasty for Acute Myocardial Infarction According to the MBG

<table>
<thead>
<tr>
<th>Variables</th>
<th>MBG 0 and 1 (%) (n=101)</th>
<th>MBG 2 and 3 (%) (n=823)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD-related MI</td>
<td>65 (64)</td>
<td>388 (47)</td>
<td>0.001</td>
</tr>
<tr>
<td>TIMI 3 before</td>
<td>4 (4)</td>
<td>146 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MVD</td>
<td>69 (68)</td>
<td>394 (46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; MI, myocardial infarction; and MVD, multivessel disease.
were older (63±12 years versus 60±12 years, \( P<0.05 \)), more often had anterior myocardial infarction (68% versus 47%, \( P<0.001 \)), and more often were diabetic (17% versus 10%, \( P=0.04 \)) but less often were smokers (37% versus 51%, \( P=0.005 \)). The percentage of referred patients (49% versus 41%, \( P=0.12 \)) and ischemic time (260±192 versus 234±140 minutes, \( P=0.12 \)) was not significantly different between both groups (see Table 1). Patients with MBG 0 or 1 grade had different angiographic variables compared with patients with MBG 2 or 3. Patients with reduced blush grade had more left anterior descending artery–related myocardial infarction (64% versus 47%, \( P<0.001 \)), more often suffered from multivessel coronary artery disease (68% versus 48%, \( P<0.001 \)), and less often had TIMI 3 flow before angioplasty (4% versus 18%, \( P<0.001 \), see Table 2). Mortality rate at follow-up was 13% in the patients with MBG 0 or 1 and 3% in the patients with MBG 2 or 3 (RR, 4.7; 95% CI, 2.3 to 9.5; \( P<0.001 \)) (see Figure 2). Kaplan-Meier curves for overall survival are shown in Figure 3. The combined incidence of death and nonfatal recurrent myocardial infarction was higher in the group with MBG 0 or 1 (33% versus 21%; RR, 1.8; 95% CI, 1.1 to 2.8; \( P=0.009 \)) (Figure 4). Evidence of more severe myocardial damage in the group with reduced blush was demonstrated by a significantly lower residual left ventricular ejection fraction (37.7±10.6 versus 43.8±11.1, \( P<0.001 \)) and larger enzymatic infarct size (LDHQ48: 1437±2388 versus 809±1672, \( P=0.001 \)) compared with the patients with MBG 2 or 3 (see Table 3). Multivariate analysis was performed to study the predictive value of angiographic variables as risk factors of death at follow-up. This analysis shows that MBG was the most important angiographic predictor of long-term mortality (see Table 4).

**Discussion**

The main finding of our study is that MBG after primary angioplasty for acute myocardial infarction is an important prognostic feature and should be added to the commonly used TIMI flow grading to define successful angiographic reperfusion with primary angioplasty for acute myocardial infarction.

Patients with TIMI 3 flow after primary angioplasty have successful angioplasty, according to the current definition. However, it has been described that “some TIMI 3 flow patients are more equal than other TIMI 3 flow patients” (reference 2, p 670) and that myocardial reperfusion is not always achieved in patients with successful angioplasty. Using the MBG, we were able to detect a group of patients with reduced myocardial reperfusion despite normal flow in the epicardial infarct-related coronary artery. This patient group consisted of 11% of the total study population. Patients with MBG 0 or 1 had a higher mortality compared with patients with MBG 2 or 3 (13% versus 3%; RR, 4.7; 95% CI, 2.3 to 9.5; \( P<0.001 \)). Also, the combined incidence of death, recurrent myocardial infarction, or revascularization was higher in the group with MBG 0 or 1 (33% versus 21%; RR, 1.8; 95% CI, 1.1 to 2.8; \( P=0.009 \)).

The patients with MBG 0 or 1 not only had a higher mortality but also had a larger infarct size. Infarct size was measured by the cumulative enzyme release for 48 hours and residual ejection fraction. Both of these 2 measurements revealed larger infarct size in patients with MBG 0 or 1 (see Table 3). This clearly relates MBG 0 or 1 grade to poor myocardial reperfusion at tissue level, therefore resulting in more enzyme release during 48 hours and in a lower residual

**TABLE 3. Infarct Size of Patients With TIMI 3 Flow After Angioplasty for Acute Myocardial Infarction According to the MBG**

<table>
<thead>
<tr>
<th>MBG 0 and 1 (n=101)</th>
<th>MBG 2 and 3 (n=823)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>37.7±10.6</td>
<td>43.8±11.1</td>
</tr>
<tr>
<td>LDHQ48, %</td>
<td>1437±2388</td>
<td>809±1672</td>
</tr>
</tbody>
</table>

* LVEF indicates left ventricular ejection fraction.
left ventricular ejection fraction. Some of the baseline characteristics are different between both groups. These potential confounders merit additional scrutiny. For example, the patients with MBG 0 or 1 are significantly older, more often have anterior myocardial infarction, and more often have diabetes compared with patients with MBG 2 or 3.

Smoking has been associated with more extensive thrombus formation.21,22 Distal plugging of thrombus has been suggested to play a role in no reflow. Therefore, the group with MBG 0 or 1 (or worse myocardial reperfusion) might consist of a higher percentage of smokers. However, there were fewer smokers in the patient group with MBG 0 or 1. This may be related to the smokers’ paradox.23–25 In our study, patients with MBG 0 or 1 grade were significantly older, confirming that age may be more important in myocardial reperfusion. The no reflow phenomenon, one of the possible factors involved in poor myocardial reperfusion, is associated with a longer ischemic time,26 but in our study there was no significant difference in mean ischemic time between patients with MBG 0 or 1 compared with patients with MBG 2 or 3. Some angiographic variables are important predictors of infarct size, and long-term survival and several angiographic variables were differently distributed in both groups. Anterior myocardial infarction is related to larger myocardial infarct size and higher long-term mortality compared with non–anterior-related myocardial infarctions.27,28 and in the patients with MBG 0 or 1, more patients had left anterior-related myocardial infarction. Patients with TIMI 3 flow on acute angiography before primary angioplasty are known to have smaller infarct size and low long-term mortality.29,30 Patients with MBG 0 or 1 had less TIMI 3 flow before angioplasty.

Patients with single-vessel disease have lower mortality compared with patients with multivessel disease,31,32 and in our study the percentage of patients with multivessel coronary artery disease was higher in the group with MBG 0 or 1. In our study, these 3 angiographic variables were unequally distributed in the groups with different MBG. Therefore, we performed multivariate analysis to study whether these angiographic variables were independent risk factors of mortality during follow-up. This analysis revealed that most of these variables were independent predictors of long-term mortality. The MBG was the strongest predictor for mortality, with a RR of 2.9 (95% CI, 1.4 to 5.8; P = 0.003), even when corrected for multivessel coronary artery disease, infarct-related artery, and TIMI 3 flow before angioplasty (see Table 4).

In our study, the incidence of patients with MBG 0 or 1 was 11%. Stone et al39 studied the value of the MBG according to the same definition in a cohort of 173 patients and found that 30.2% had MBG 0 or 1. However, in these 173 patients, only 94.2% of the patients had TIMI 3 after PCI, and 39% of the PCI procedures were performed after failed thrombolysis as a rescue PCI procedure. We studied the value of MBG in 924 patients, all with TIMI 3 after PCI, and all patients underwent primary PCI; no patients in our study underwent PCI after failed thrombolysis. Subsequently, at least in part, the ischemic time in the study by Stone et al population was importantly longer. Mean ischemic time in the report by Stone et al was $314 \pm 184$ minutes (MBG 3) and $359 \pm 216$ minutes (MBG 0 to 2), and ischemic time in our study was $260 \pm 192$ minutes (MBG 2 or 3) and $234 \pm 140$ minutes (MBG 0 or 1). Furthermore, in the study by Stone et al, additional PCI procedures (atherectomy and laser) were performed in 11.6% of the patients, indicating that PCI procedure with balloon and stenting were not sufficient to achieve optimal angiographic result. Our study included patients treated with only balloon angioplasty or intracoronary stenting. These above-mentioned differences in study populations account for the higher incidence of patients with MBG 0 or 1 in Stone’s study, because his study population had a higher risk of not achieving reperfusion at the myocardial level.

The Myocardial Blush Grade

The arrival of radiographic contrast agents in the distal microvasculature of the downstream myocardium after passage of the epicardial coronary artery has been previously studied with semiquantitative techniques based on densitometry.33,34 These semiquantitative methods have also been applied in the setting of acute myocardial infarction35 but are cumbersome, time consuming, and difficult to apply in routine clinical practice. However, qualitative visual assessment is feasible and applicable in routine clinical practice, because reproducibility and the variability of this method allow its use in clinical practice until more sophisticated techniques have been proven to be superior. Additional research will be needed to study whether the use of semiquantitative techniques enhances the predictive value of angiographic data. In our definition, rapidity of the appearance of the myocardial blush plays no role as it does in the TIMI perfusion grade definition. Therefore, we did not study its value in this prospective study. However, both methods clearly have the possibility to distinguish a low-risk group (MBG 2 or 3).

**Conclusion**

In patients with TIMI 3 flow after angioplasty, 11% have a MBG 0 or 1. These patients have larger enzymatic infarct size, lower residual ejection fraction, higher mortality, and higher incidence of MACE. This angiographic feature has important clinical value, because MBG 0 or 1 identifies patients with a >4-fold higher risk of death during long-term follow-up.

**References**

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