Thrombolysis In Myocardial Infarction Myocardial Perfusion Grade in Angiography Correlates With Myocardial Salvage in Patients With Acute Myocardial Infarction Treated With Stenting or Thrombolysis

Alban Dibra, MD,* Julinda Mehilli, MD,* Josef Dirschinger, MD,* Jürgen Pache, MD,* Jodi Neverve, BS,† Markus Schwaiger, MD,† Albert Schömig, MD,* Adnan Kastrati, MD*
Munich, Germany

OBJECTIVES
We sought to assess the relationship between the Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion (TMP) grade and myocardial salvage as well as the usefulness of TMP grade in comparing two different reperfusion strategies.

BACKGROUND
The angiographic index of TMP grade correlates with infarct size and mortality after thrombolysis for acute myocardial infarction (AMI). Its relationship to myocardial salvage and its usefulness in comparing different reperfusion strategies are not known.

METHODS
We analyzed the TMP grade on angiograms obtained at one to two weeks after treatment in 267 patients enrolled in two randomized trials that compared stenting with thrombolysis in AMI. Patients were classified into two groups: 159 patients with TMP grade 2/3 and 108 patients with TMP grade 0/1. Two scintigraphic studies were performed: before and one to two weeks after reperfusion. The salvage index was calculated as the proportion of the area at risk salvaged by reperfusion.

RESULTS
Patients with TMP grade 2/3 had a higher salvage index (0.49/ 0.42 vs. 0.34/ 0.49, p < 0.01), a smaller final infarct size (15.4/ 15.5% vs. 22.1/ 16.2% of the left ventricle, p = 0.001), and a trend toward lower one-year mortality (3.8% vs. 8.3%, p = 0.11) than patients with TMP grade 0/1. The relationship between TMP and salvage index was independent of the form of reperfusion therapy. The proportion of patients with TMP grade 2/3 was significantly higher after stenting than after thrombolysis (70.9% vs. 48.1%, p < 0.001).

CONCLUSIONS
These findings show that the TMP grade is a useful marker of the degree of myocardial salvage achieved with reperfusion and a sensitive indicator of the efficacy of reperfusion strategies in patients with AMI.

The current concept of optimal reperfusion in acute myocardial infarction (AMI) includes not only the rapid and sustained restoration of blood flow in the epicardial artery, but also the restoration of perfusion at the tissue level within the jeopardized myocardium (1). The failure to achieve an adequate blood supply at this level has been associated with a greater infarct size, poor left ventricular (LV) function and remodeling, congestive heart failure, and higher mortality, despite the presence of a patent infarct-related artery (IRA) (2,3). The cause of the no-reflow phenomenon has been attributed to microvascular dysfunction (4), which is a complex phenomenon that initiates with the onset of ischemia and extends up to 48 h afterward.

Several diagnostic techniques have been employed to evaluate tissue-level microvascular perfusion in the last decade. Studies using myocardial contrast echocardiography, magnetic resonance, Doppler flow wire, nuclear imaging, ST-segment resolution, myocardial blush, and corrected Thrombolysis In Myocardial Infarction (TIMI) frame count have provided investigators with information on the incidence of no-reflow and its clinical consequences in patients with abnormal perfusion at tissue-level myocardium (2,5–10). Recently, Gibson et al. (11) introduced a new angiographic index—TIMI myocardial perfusion (TMP) grade—as a predictor of mortality in patients with AMI. Although the TMP grade correlates with the final infarct size in patients with AMI treated with thrombolysis (12), it is still unclear whether this index also reflects the degree of myocardial salvage produced by various reperfusion strategies. The aim of our study was to assess whether the TMP grade may serve as an angiographic marker of myocardial salvage achieved with stenting or thrombolysis in patients with AMI and, consequently, as an indicator of reperfusion efficacy.

METHODS
The Stent versus Thrombolysis for Occluded coronary arteries in Patients with Acute Myocardial Infarction (STOPAMI)-1 and -2 were two randomized trials that
compared stenting with thrombolysis in 302 patients with AMI within the first 12 h from symptom onset (13,14). Details of the inclusion criteria and reperfusion regimen have been published previously (13,14). In brief, stenting was always combined with abciximab, and thrombolysis consisted of either full-dose alteplase alone (STOPAMI-1) or half-dose alteplase plus abciximab (STOPAMI-2) (13,14). A six-month visit to the outpatient clinic and 12-month phone contact were carried out for all patients. The protocol of both randomized studies was approved by the local Ethics Committee, and patients gave written, informed consent for participation.

**Angiographic evaluation.** A coronary angiogram was scheduled to be performed one to two weeks after randomization in all patients. Of the 290 patients who survived to this time point, 23 did not consent to planned angiography. Therefore, the angiograms of 267 patients were available for assessment of TMP grade. Of these patients, 134 had been randomized to stenting and 133 to thrombolysis (62 patients without and 71 patients with abciximab). The assessment was done in the Angiographic Core Laboratory by investigators who were unaware of the scintigraphic results or clinical outcome. We applied the grading system described by Gibson et al. (11). Briefly, in TMP grade 0, dye fails to enter the microvasculature; in TMP grade 1, dye enters but fails to exit the microvasculature (persisting on the subsequent injection); in TMP grade 2, dye enters and slowly exits the microvasculature (staining is not present on the subsequent injection); and in TMP grade 3, there is normal entry and mild persistence of dye at the end of the injection. Grades 0 and 1 of TMP were considered to indicate closed myocardium, whereas TMP grades 2 and 3 were considered to indicate open myocardium, with respect to microvascular integrity and perfusion at the myocardial tissue level (12). Assessment of TMP was done during contrast injection of either the IRA or the vessel supplying collateral channels to the IRA, in case the latter was occluded. The angiographic projections used for the evaluation of TMP grade were those that allowed for optimal visualization of the myocardial territory supplied by the IRA, without superimposition of myocardial regions supplied by non-IRAs. Anterograde flow in the IRA was assessed according to the TIMI grading system (15).

**Scintigraphic evaluation.** All patients received an intravenous injection of 27 mCi (1,000 MBq) of technetium-99m sestamibi immediately after randomization. Single-photon emission computed tomography was performed within 6 to 8 h of injection of the radionuclide to calculate the initial perfusion defect representing the area at risk. A second scintigraphic study was performed 7 to 14 days after primary treatment for calculation of the final infarct size. The salvage index was calculated as the proportion of the initial area at risk salvaged by reperfusion. Paired scintigraphic studies necessary for calculation of the salvage index were available in 248 (93%) of the 267 patients included in this study.

**Statistical analysis.** Data are presented as the mean value ± SD, counts, or percentages. The analysis consisted of a comparison between patients with TMP grade 0 or 1 (closed myocardium) and those with TMP grade 2 or 3 (open myocardium). An additional comparison was made between the two reperfusion strategies—stenting and thrombolysis. Differences between the groups, with respect to continuous variables, were compared by the two-sided t test. The two-sided chi-squared or Fisher exact test (whenever an expected cell value was <5) was used for analysis of categorical variables. The relationship between TMP grade and myocardial salvage (continuous response variable) was adjusted for other co-variates, including the reperfusion therapy option, in a multivariate model based on multiple linear regression analysis. A p value <0.05 was considered statistically significant.

**RESULTS**

Grade 2/3 TMP was found in 159 patients (62 patients with grade 2 and 97 patients with grade 3) and grade 0/1 TMP in 108 patients (58 patients with grade 0 and 50 patients with grade 1). Table 1 shows that there were no significant differences between the two groups with respect to the baseline characteristics, except for the proportion of smokers, which was higher in the group with TMP grade 2/3. TIMI flow grade 3 (complete epicardial flow restoration) was present in 90.6% of the patients with TMP grade 2/3 and in 41.7% of those with TMP grade 0/1 (p < 0.001).

**TMP grade as an indicator of myocardial salvage and clinical outcome.** Although there were no differences in the initial perfusion defect (Table 1) between the two groups, patients with TMP grade 2/3 had a significantly higher salvage index (0.49 ± 0.42 vs. 0.34 ± 0.49, p = 0.01), a smaller final infarct size (15.4 ± 15.5% vs. 22.1 ± 16.2% of the LV, p = 0.001), and a trend toward lower one-year mortality (3.8% vs. 8.3%, p = 0.11) than patients with TMP grade 0/1 (Fig. 1). In addition, the angiographic ejection fraction of the LV, available in 261 of the 267 study patients, was significantly higher among patients with TMP grade 2/3 (58.3 ± 12.7% vs. 53.1 ± 12.3% in patients with TMP grade 0/1, p = 0.001). After adjustment for other co-variates (factors shown in Table 1 plus TIMI flow...
grade), a higher TMP grade was independently correlated with a higher salvage index ($p = 0.001$). The TMP grade ranked second, immediately after the type of reperfusion therapy ($F$ value $= 11$, $p < 0.001$), as an independent predictor of myocardial salvage. In this model, the conventional TIMI flow grades showed a much weaker correlation with myocardial salvage ($p = 0.048$). In a second step, we forced the angiographic ejection fraction of the LV into the same multivariate model to assess whether the TMP grade maintains its independent predictive value for myocardial salvage after this adjustment. On the basis of the results yielded by this new model, the TMP grade continued to be a significant independent predictor of myocardial salvage ($F$ value $= 12$, $p < 0.001$).

**TMP grade as a marker of the efficacy of reperfusion therapy.** We compared stenting with thrombolysis in their ability to achieve a higher TMP grade. The proportion of patients with TMP grade 2/3 was significantly higher after stenting than after thrombolysis (70.9% vs. 48.1%, $p = 0.001$). Within the thrombolysis group, there was a higher proportion of patients with TMP grade 2/3 among those receiving the combination of alteplase plus abciximab than among those receiving alteplase alone (56.3% vs. 38.7%, $p = 0.04$). The results based on TMP grade, which showed the superiority of stenting as a reperfusion option, were concordant with the results emerging from the comparison of stenting with thrombolysis in terms of myocardial salvage and one-year mortality. Compared with thrombolysis, stenting was associated with greater myocardial salvage ($0.54 \pm 0.29$ vs. $0.30 \pm 0.55$, $p < 0.001$) and lower mortality (2.2% vs. 9.0%, $p = 0.02$). Within the thrombolysis group, there were trends toward greater salvage ($0.36 \pm 0.50$ vs. $0.23 \pm 0.60$, $p = 0.2$) and lower mortality (5.6% vs. 12.9%, $p = 0.14$) among those receiving the combination of alteplase plus abciximab than among those receiving alteplase alone.

**DISCUSSION**

This study shows, for the first time, that the TMP grade is a reliable indicator of the degree of myocardial salvage achieved with reperfusion therapy. It also enabled the identification of the reperfusion therapy with superior efficacy when stenting was compared with thrombolysis. Analysis of the TMP grade permitted even the detection of subtle differences between the two thrombolytic regimens: thrombolysis alone or combined with the glycoprotein IIb/IIIa inhibitor abciximab. Our findings provide an ex-

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TMP Grade 2/3 (n = 159)</th>
<th>TMP Grade 0/1 (n = 108)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59.8 ± 13</td>
<td>62.1 ± 12</td>
<td>0.13</td>
</tr>
<tr>
<td>Women</td>
<td>45 (28.3%)</td>
<td>23 (20.9%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Current smoker</td>
<td>85 (52.8%)</td>
<td>44 (40.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (20.2%)</td>
<td>19 (17.3%)</td>
<td>0.60</td>
</tr>
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<td>Hypercholesterolemia</td>
<td>108 (69.1%)</td>
<td>78 (71.8%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>97 (61.4%)</td>
<td>72 (67.1%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>16 (9.9%)</td>
<td>16 (15.2%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Previous bypass surgery</td>
<td>5 (3.1%)</td>
<td>6 (5.6%)</td>
<td>0.50*</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>92 (58.0%)</td>
<td>69 (64.3%)</td>
<td>0.32</td>
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<tr>
<td>Killip class &gt;2</td>
<td>7 (4.4%)</td>
<td>4 (3.7%)</td>
<td>0.96*</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>72 (45.2%)</td>
<td>56 (51.7%)</td>
<td>0.29</td>
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<tr>
<td>Peak CK (IU/ml)</td>
<td>973.4 ± 1199</td>
<td>1,117.3 ± 975</td>
<td>0.30</td>
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<tr>
<td>Symptom onset-to-treatment interval (min)</td>
<td>240.8 ± 158</td>
<td>270.2 ± 171</td>
<td>0.29</td>
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<td>Initial perfusion defect (% of left ventricle)</td>
<td>31.1 ± 19.5</td>
<td>33.9 ± 19.4</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Fisher exact test. Data are presented as the mean ± SD or number (%) of patients.

CK = creatine kinase; TMP = TIMI myocardial perfusion.

**Figure 1.** Mean myocardial salvage index, mean final infarct size, and one-year mortality in patients with TIMI myocardial perfusion (TMP) grade 2/3 versus grade 0/1. LV = left ventricle.
plan for the smaller infarct size (12) and better survival (11,16) found in patients with AMI with higher TMP grades after thrombolysis.

Several parameters have been proposed for the assessment of reperfusion success in patients with AMI (17). Parameters that reflect flow restoration not only in large epicardial arteries but also in the microcirculation bed are being investigated with increasing interest (18). New angiographic indexes have been proposed for more reliable assessment of reperfusion at the myocardial tissue level (9–11). Although recent findings support the prognostic value of these indexes (9–11), the exact underlying mechanisms are not clear. Patients with TMP grade 2/3 after thrombolysis had a smaller infarct size on scintigrams recorded >120 h after treatment (12). However, the significance of a high TMP grade in terms of myocardial salvage remains unknown. Our study protocol provided us with paired scintigraphic studies (baseline and follow-up) which are required for the calculation of myocardial salvage. It also allowed the comparison of the two most commonly used reperfusion strategies—thrombolysis and stenting—based on the TMP grading system.

In contrast to other studies, which assessed the TMP grade or blushing score on coronary angiograms obtained shortly after reperfusion therapy (9,11,12,16), we used coronary angiograms performed at one to two weeks after primary treatment for the assessment of TMP grade. This interval was chosen so that all patients would have final angiographic and scintigraphic assessments of reperfusion success very close to each other. This strategy minimizes the chance for new events to occur between angiographic and scintigraphic evaluations (e.g., vessel re-occlusion), with the risk of introducing a bias in the relationship analysis. In addition, assessing the TMP grade means assessing the status of the coronary microvasculature, which, during AMI, undergoes a series of changes leading to microvascular dysfunction. Microvascular dysfunction is considered to result from both ischemic injury and atheroembolism, which develop in the first 1 to 2 h of AMI, and reperfusion injury, which initiates after the restoration of blood flow in the IRA and lasts up to 48 h after AMI onset (4). Neumann et al. (19) have reported that both basal and peak flow velocities increased at two weeks, compared with values obtained immediately after percutaneous coronary revascularization in patients with AMI. In the same line, Ito et al. (20), who used myocardial contrast echocardiography to assess the temporal changes in myocardial perfusion after reflow, showed that contrast peak intensity in the late stage of infarction might be a more useful estimate of myocardial viability than contrast peak intensity at day 1. Therefore, the TMP grade measured at one to two weeks after primary treatment of AMI might more accurately reflect the "final" status of microvascular function. Inherent to our strategy of assessing the TMP grade at one to two weeks after the acute event is the limitation that the validity of the results may be restricted to those patients with AMI surviving this interval;

we are unable to provide data on patients who died before the day of scheduled angiography. However, our specific objective was to determine the potential relationship between the TMP grade by angiography and myocardial salvage by scintigraphy, rather than the assessment of the prognostic value of TMP grade, which has already been demonstrated in previous studies (11). The number of patients enrolled in the STOPAMI-1 and -2 trials was relatively limited for analyses based on mortality.

Reprint requests and correspondence: Dr. Adnan Kastrati, Deutsches Herzcentrum München, Lazaretstr. 36, 80636 Munich, Germany. E-mail: kastrati@dhm.mhn.de.

REFERENCES


