Relationship of TIMI Myocardial Perfusion Grade to Mortality After Administration of Thrombolytic Drugs

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Background — Although improved epicardial blood flow (as assessed with either TIMI flow grades or TIMI frame count) has been related to reduced mortality after administration of thrombolytic drugs, the relationship of myocardial perfusion (as assessed on the coronary arteriogram) to mortality has not been examined.

Methods and Results — A new, simple angiographic method, the TIMI myocardial perfusion (TMP) grade, was used to assess the filling and clearance of contrast in the myocardium in 762 patients in the TIMI (Thrombolysis In Myocardial Infarction) 10B trial, and its relationship to mortality was examined. TMP grade 0 was defined as no apparent tissue-level perfusion (no ground-glass appearance of blush or opacification of the myocardium) in the distribution of the culprit artery; TMP grade 1 indicates presence of myocardial blush but no clearance from the microvasculature (blush or a stain was present on the next injection); TMP grade 2 blush clears slowly (blush is strongly persistent and diminishes minimally or not at all during 3 cardiac cycles of the washout phase); and TMP grade 3 indicates that blush begins to clear during washout (blush is minimally persistent after 3 cardiac cycles of washout). There was a mortality gradient across the TMP grades, with mortality lowest in those patients with TMP grade 3 (2.0%), intermediate in TMP grade 2 (4.4%), and highest in TMP grades 0 and 1 (6.0%; 3-way \( P < 0.05 \)). Even among patients with TIMI grade 3 flow in the epicardial artery, the TMP grades allowed further risk stratification of 30-day mortality: 0.73% for TMP grade 3; 2.9% for TMP grade 2; 5.0% for TMP grade 0 or 1 (\( P = 0.03 \) for TMP grade 3 versus grades 0, 1, and 2; 3-way \( P = 0.066 \)). TMP grade 3 flow was a multivariate correlate of 30-day mortality (OR 0.35, 95% CI 0.12 to 1.02, \( P = 0.054 \)) in a multivariate model that adjusted for the presence of TIMI 3 flow (\( P = \text{NS} \)), the corrected TIMI frame count (OR 1.02, \( P = 0.06 \)), the presence of an anterior myocardial infarction (OR 2.3, \( P = 0.03 \)), pulse rate on admission (\( P = \text{NS} \)), female sex (\( P = \text{NS} \)), and age (OR 1.1, \( P < 0.001 \)).

Conclusions — Impaired perfusion of the myocardium on coronary arteriography by use of the TMP grade is related to a higher risk of mortality after administration of thrombolytic drugs that is independent of flow in the epicardial artery. Patients with both normal epicardial flow (TIMI grade 3 flow) and normal tissue level perfusion (TMP grade 3) have an extremely low risk of mortality. (Circulation. 2000;101:125-130.)

Key Words: mortality ■ risk factors ■ perfusion ■ thrombolysis

Whereas improved epicardial blood flow (as assessed with either TIMI flow grades\(^1-6\) or the TIMI frame count\(^7,8\)) has been related to reduced mortality after administration of thrombolytic drugs, the relationship between tissue-level microvascular perfusion and mortality has not been examined in a large number of patients after thrombolytic administration. This study describes the development and use of a simple semiquantitative classification scheme, the TIMI myocardial perfusion grade (TMP), that can be used to characterize the filling and clearance of myocardial perfusion from a coronary angiogram. This filling appears as a myocardial blush, the ground-glass appearance of the myocardium on the coronary arteriogram. We hypothesized that improved myocardial perfusion would be related to lower mortality and that the assessment of myocardial perfusion would add independent prognostic information to the assessment of epicardial flow.

Methods

Seven hundred sixty two patients from the TIMI (Thrombolysis In Myocardial Infarction) 10B trial had both TMP and 30-day mortality data available for analysis. TIMI 10B was a randomized comparison...
TABLE 1. Definitions of TMP Grades

<table>
<thead>
<tr>
<th>TMP Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Failure of dye to enter the microvasculature. Either minimal or no ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.</td>
</tr>
<tr>
<td>1</td>
<td>Dye slowly enters but fails to exit the microvasculature. There is the ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (~30 seconds between injections).</td>
</tr>
<tr>
<td>2</td>
<td>Delayed entry and exit of dye from the microvasculature. There is the ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (ie, dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).</td>
</tr>
<tr>
<td>3</td>
<td>Normal entry and exit of dye from the microvasculature. There is the ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent at the end of the washout phase (ie, dye is gone or is mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3.</td>
</tr>
</tbody>
</table>

of TNK (30, 40, and 50 mg) and 90-minute infusion of recombinant tissue plasminogen activator (alteplase) in 854 patients.9 Angiography was performed at 90 minutes after thrombolytic administration.9 Nitroglycerin was administered every 15 minutes if the systolic blood pressure exceeded 110 mm Hg.9

Assessment of Flow
All angiographic end points were prospectively assessed at 90 minutes. The TIMI flow grade, as previously defined,1 was assessed at the TIMI angiographic core laboratory by a single observer (C.M.G.) who was blinded to treatment assignment and clinical outcome. The corrected TIMI frame count (CTFC) is the number of cine frames required for contrast to first reach standardized distal coronary landmarks in the culprit artery and is measured by use of a frame counter on a cine viewer.7,8 A frame count of 100, a value that is the 99th percentile of patent vessels, was imputed to an occluded vessel.7,9 The CTFC is a measure of time, and the data were converted when necessary to be based on the most common filming speed in the United States of 30 frames per second.7,8 The collateral grade was assessed at 90 minutes10 and was based on the presence of collaterals to the culprit artery.

TMP grades are defined in Table 1. Blush was assessed distal to the culprit lesion, and views were chosen to minimize superimposition of noninfarcted territories in the assessment of the TMP grade for the culprit artery. The duration of cine filming was required to exceed 3 cardiac cycles in the washout phase to assess washout of the myocardial blush. Care was taken not to mistake filling of the venous system, such as the great cardiac vein, as blush. Blush was assessed during the same phase of the cardiac cycle, because it may be less intense during diastole. Mortality was confirmed by a clinical events committee.

Statistical Analysis
Analyses were performed with Stata statistical software version 6.0.11 Variables were compared with the Fisher’s exact test or χ² test for categorical data. The Student’s t test or ANOVA was used for analysis of normally distributed continuous variables. The nonparametric Wilcoxon rank sum test (for 2-way comparisons) or the Kruskal-Wallis test (for 3-way comparisons) was used to compare continuous variables when the data were not normally distributed or when data were imputed to an occluded vessel. Data are summarized as mean±SD.

Results
Baseline Demographic and Angiographic Characteristics of the TMP Grades
There was no difference among TMP grades with respect to many demographic and angiographic variables: age, sex, blood pressure, pulse rate, ejection fraction, history of myocardial infarction (MI), and presence of angiographically visible collaterals (Tables 2 and 3). Compared with patients who exhibited some myocardial perfusion (TMP grades 1, 2, or 3), patients without detectable perfusion (TMP grade 0) had significantly slower epicardial flow (higher CTFCs and a lower incidence of TIMI grade 3 flow), a significantly greater thrombus burden, and tighter epicardial stenoses (Table 3). In these cases, LAD infarcts tended to be involved more frequently (Table 3).

Relationship of TMP Grade to Mortality
Patients with TMP grade 0 had a higher 30-day mortality rate (6.2%, 27 of 434 patients) than patients with TMP grade 1 (5.1%, 4 of 79 patients), TMP grade 2 (4.4%, 2 of 46

TABLE 2. Baseline Characteristics by TMP Grade

<table>
<thead>
<tr>
<th></th>
<th>No Myocardial Perfusion (TMP 0)</th>
<th>Myocardial Perfusion (TMP 1/2/3)</th>
<th>P (Grade 0 vs 3/2/1)</th>
<th>TMP Grade 1</th>
<th>TMP Grade 2</th>
<th>TMP Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>434</td>
<td>328</td>
<td></td>
<td>79</td>
<td>46</td>
<td>203</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.7±11.7</td>
<td>59.3±12.0</td>
<td>NS</td>
<td>58.8±11.2</td>
<td>59.3±13.2</td>
<td>59.4±12.1</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>77.4</td>
<td>72.6</td>
<td>NS</td>
<td>73.4</td>
<td>69.6</td>
<td>72.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134.8±22.6</td>
<td>134.1±21.5</td>
<td>NS</td>
<td>132.2±21.0</td>
<td>135.8±22.0</td>
<td>134.4±21.7</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79.3±16.1</td>
<td>78.7±15.2</td>
<td>NS</td>
<td>78.9±13.3</td>
<td>76.3±12.9</td>
<td>79.1±16.3</td>
</tr>
<tr>
<td>Pulse, bpm</td>
<td>75.6±17.6</td>
<td>75.8±16.6</td>
<td>NS</td>
<td>76.9±15.7</td>
<td>74.3±16.5</td>
<td>75.7±17.0</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>57.6±14.3</td>
<td>57.7±14.9</td>
<td>NS</td>
<td>53.7±15.5</td>
<td>59.5±13.4</td>
<td>58.6±14.9</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>16.9</td>
<td>12.9</td>
<td>NS</td>
<td>10.3</td>
<td>21.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Nitroglycerin use, %</td>
<td>88.9</td>
<td>88.1</td>
<td>NS</td>
<td>86.1</td>
<td>91.3</td>
<td>88.2</td>
</tr>
<tr>
<td>Aspirin use within 24 h of treatment, %</td>
<td>96.5</td>
<td>96.7</td>
<td>NS</td>
<td>93.7</td>
<td>95.7</td>
<td>98.0</td>
</tr>
</tbody>
</table>

All P=NS, including comparisons among TMP grades 1, 2, and 3 and TMP grade 3 vs all others.
patients), or TMP grade 3 (2.0%, 4 of 203 patients; TMP grades 0 and 1 combined to achieve adequate power, \( P = 0.055 \) by Fisher’s exact test, \( P = 0.046 \) by logistic regression) (Figure 1). Likewise, when TMP grades 2 and 3 flow were combined, the mortality rate was lower than that in patients with TMP grade 0 or 1 (2.4% [6 of 249 patients] versus 6.0% [31 of 513 patients]; \( P = 0.03 \)).

Risk Stratification Within TIMI Grade 3 Flow by Use of TMP Grades

Among patients with TIMI grade 3 flow in the epicardial artery, use of TMP grades allowed further risk stratification such that reduced myocardial perfusion was related to a higher risk of 30-day mortality: the mortality rate was 0.7% among those with TMP grade 3 (1/137) versus 4.7% among all others (15/318; \( P = 0.05 \)) (Figure 2). When the patients were further divided into 3 TMP grades, the same relationship held true: the mortality rate was 0.73% for TMP grade 3, 2.9% for TMP grade 2, and 5.0% for TMP grades 0 and 1 (\( P = 0.03 \) for TMP grade 3 versus grades 0, 1, and 2; 3-way \( P = 0.066 \)) (Figure 2). For an open (TMP grade 2 or 3) versus a closed (TMP grade 0 or 1) microvasculature, the value was 0.04. Among those patients with less than TIMI grade 3 flow in the epicardial artery, those with TMP grade 3 flow also tended to have better outcomes (Figure 2). Likewise, among patients with a CTFC of <40 (a value that quantitatively characterizes TIMI grade 3 flow), \( P = 0.0001 \). TMP grade 3 was associated with reduced mortality (0.8%, 1 of 131 patients) compared with TMP grades 0 through 2 (4.5%, 14 of 306 patients; \( P = 0.05 \)) (Figure 3). A similar gradient was seen in patients with CTFC \( \geq 40 \), with a 4.5% (3/67) mortality rate in TMP grade 3 compared with 7.8% (18/232) in TMP grades 0 through 2 (4-way \( P = 0.02 \)) (Figure 3).

To evaluate the independent contribution of myocardial perfusion to mortality, a multivariate model was developed that included angiographic and demographic variables previously shown to be related to mortality.\(^8\) The presence of TMP grade 3 flow was an independent correlate of 30-day mortality (OR 0.35, 95% CI 0.12 to 1.02, \( P = 0.054 \)) in a multivariate model that adjusted for variables that have been previously identified in the TIMI studies as correlates of mortality\(^8\): TIMI grade 3 flow (\( P = \text{NS} \)), CTFC (OR 1.02 per 1-frame rise, \( P = 0.06 \)), presence of an anterior MI (OR 2.3, \( P = 0.03 \)), pulse rate on admission (\( P = \text{NS} \)), female sex (\( P = \text{NS} \)), and age (OR 1.1 per 1-year rise, \( P < 0.001 \)).

![Figure 1. Relationship between myocardial perfusion grade and mortality.](image-url)

**Figure 1.** Relationship between myocardial perfusion grade and mortality. Mortality increases in a stepwise fashion with decreasing TMP grades. Three-way \( P \) value by Fisher’s exact test (TMP grades 0 and 1 combined to achieve adequate power) was 0.055; by logistic regression, it was 0.046. Mortality for TMP grade 3 was significantly lower than in TMP grades 0 through 2 combined (\( P = 0.028 \)), and that for TMP grade 0/1 (31 [6.0%] of 513 patients) was greater than that of TMP grade 2/3 (6 [2.4%] of 249 patients) (\( P = 0.03 \)).
Combination of TIMI Epicardial Flow and TMP Grades and Their Relationship to Mortality

Those patients with both epicardial TIMI grade 3 flow and myocardial perfusion grade 3 flow (successful epicardial and tissue-level perfusion) had a low mortality rate of 0.73% (1/137), whereas those with grades of 0 or 1 for both TIMI epicardial flow and myocardial perfusion had a mortality rate of 10.9% (14 of 129 patients) (Figure 4). Patients with either incomplete epicardial or myocardial flow (ie, patients with neither the combination of TIMI flow grade 3 and TMP grade 3 or the combination of TIMI flow grade 0/1 and TMP grade 0/1) had an intermediate mortality rate of 4.4% (21/483; 3-way \( P \approx 0.001 \)) (Figure 4). The presence of both TIMI epicardial flow and myocardial perfusion grade 3 (successful epicardial and tissue-level reperfusion) was a multivariate predictor of low mortality (OR 0.056, \( P \approx 0.006 \)), even after adjustment for anterior MI location and age (overall model \( n=742, P<0.0001 \)). Thus, in the multivariate model, the odds of death by 30 days for patients with an occluded epicardial artery and no tissue-level reperfusion (TIMI flow grade 0/1 and TMP grade 0/1) were 18 times as great as in those with both successful epicardial and successful tissue-level reperfusion (TIMI flow grade 3 and TMP grade 3).

Discussion

Improved epicardial blood flow assessed by use of either TIMI flow grades\(^1\)–\(^6\) or the TIMI frame count\(^7\)\(^8\) has been related to reduced mortality after thrombolytic administra-
tion. The data presented here indicate that improved myocardial perfusion at 90 minutes after thrombolytic administration is related to reduced mortality independent of epicardial blood flow. Its reliance on ordinary visual inspection of the angiogram without the use of sophisticated equipment allows the method to be conveniently and broadly applied. Although simple, the myocardial perfusion grade scheme is semiquantitative and is adjusted for the heart rate of the patient. These findings extend those of previous investigators\(^1\)–\(^6\) who have reported that patients with TIMI grade 3 flow have a reduced incidence of mortality. Use of the TMP grades allows additional risk stratification into low- and high-risk subgroups such that slower myocardial perfusion among patients with TIMI grade 3 flow is related to higher mortality (0.7% for TMP grade 3 versus 4.7% for TMP grades 0 to 2; \( P=0.03 \) for TMP grade 3 vs grades 0 through 2; 3-way \( P=0.066 \)). Likewise, among patients with epicardial TIMI grades 0 through 2 flow, mortality tended to be lower in the TMP grade 3 group (4.7% vs 7.4% for TMP grades 0 through 2; \( P=\text{NS} \)).
Finally, the combined use of the TMP grade and the TIMI flow grade appears to identify 2 subgroups of patients with extremely low and high risks of mortality, respectively. Patients with both normal epicardial flow and myocardial perfusion (both grade 3) had a mortality rate of 0.73%. As we have reported in the past, patients with hyperemic flow (CTFCs faster than the 95th percentile, 14 frames, TIMI grade 4 flow) were found to have a mortality rate of 0% (0/41), and these patients had nearly twice the incidence of excellent myocardial perfusion (TMP grade 3) as other groups (44.8% versus 26.2%; \( P = 0.03 \)). Improved myocardial perfusion may explain in part the favorable mortality rate that we have reported for this subgroup of patients. Thus, the TMP grade adds additional prognostic information to the conventional epicardial TIMI flow grades and TIMI frame counts.

**Relationship to Previous Work in the Field**

Van’t Hof et al showed that the presence of no, minimal, moderate, or normal blush (relative to the contrast density in uninvolved territories) is related to mortality after primary angioplasty. The method used in the present study differs from that study in that we characterize the duration of the blush rather than the brightness or density of the blush. The patients in the present study were treated with thrombolysis, whereas those in the study by Van’t Hof et al were treated with primary PTCA. Thus, it appears that both the contrast density and the duration of blush may be related to mortality, but both measures have not been implemented simultaneously in the same study to determine whether they are independent of one another.

Myocardial contrast echocardiography (MCE) has also been used to characterize the no-reflow phenomenon. The incidence of no reflow varies across studies. Whereas we observed that nearly half of the patients had minimal or no blush on the coronary arteriogram, prior reports have ranged from 23% to 56% of patients having no-reflow after restoration of patency (via either thrombolytic administration or primary PTCA) when MCE was used. The lower percentages in some MCE studies likely reflect the lower number of patients with no reflow after patency is restored, whereas our series includes patients with occluded epicardial arteries. In
the study by Ito et al,13 patients were excluded if they had a tight residual stenosis, and 29 of 39 patients were treated with primary PTCA.

Myocardial tissue perfusion has also been assessed by Maes et al17 using PET. Among patients with TIMI grade 3 epicardial flow, both regional and global ejection fraction at 5 days and 3 months after infarction were lower in patients with severely impaired myocardial flow than in patients with moderately decreased flow or adequate tissue reperfusion. This reduced contractile function may explain in part the mortality risk observed in patients with TMP grades 0 or 1.

Study Limitations

TMP grades were available in 88% of patients with 30-day mortality data in the TIMI 10B trial (762 of 865 patients). With prospective emphasis on a longer duration of cine filming, adequate panning, and the use of a 9-in image intensifier in coronary angiography, it is likely that the rate of ascertainment will be greater. The mortality rate among patients in whom TMP grades were assessed (4.9%, 37 of 762 patients) was no different from that in the study group overall (5.3%, 46 of 865 patients). The reproducibility of the TMP grades remains to be determined. It must be borne in mind that although 90-minute myocardial perfusion and epicardial coronary blood flow are both related to mortality, there are other causes of death that may be unrelated to 90-minute perfusion, such as intracranial hemorrhage, reinfarction, ventricular arrhythmias, and mechanical complications. Both rescue and adjunctive angioplasty may have obscured differences in outcomes that would have been attributable to 90-minute TIMI flow grades and TMP grades. However, even when the analysis was stratified by those patients who did not subsequently undergo rescue or adjunctive PTCA or stenting and those who did, the same relationships were observed (3-way P = 0.003 and P = 0.088, respectively).

Conclusions

After administration of thrombolytic drugs in patients with acute MI, impaired perfusion of the myocardium on coronary arteriography as assessed by TMP grade is related to a higher risk of mortality that is independent of flow in the epicardial artery. The use of the TMP grade permits risk stratification, even among patients with TIMI grade 3 flow. Patients with both normal epicardial flow (TIMI grade 3 flow) and normal tissue-level perfusion (TMP grade 3 flow) had an extremely low risk of mortality (0.73%) and in a multivariate model were 18 times less likely to die by 30 days than patients with occluded epicardial flow (TIMI grade 0 or 1 flow) and no tissue perfusion (TMP grade 0 or 1). The TMP grade represents a simple, readily available method to assess myocardial perfusion in patients undergoing reperfusion therapy.

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References


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