TIMI Myocardial Perfusion Grade and ST Segment Resolution: Association With Infarct Size as Assessed by Single Photon Emission Computed Tomography Imaging

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Background—The TIMI myocardial perfusion grade (TMPG) and ST-segment resolution both reflect perfusion and are associated with mortality after thrombolysis for acute myocardial infarction. We hypothesized that these measures would also be associated with infarct size by single photon emission computed tomography (SPECT).

Methods and Results—In the LIMIT AMI trial (Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction) of lytic monotherapy versus lytic plus rhuMAb CD18, early 90-minute TMPG (n=221) and ST segment resolution (n=242) were compared with subsequent SPECT Technetium-99 m Sestamibi, measuring the percentage of the left ventricle with no Sestamibi uptake. Infarct sizes were larger with TMPG 0 or 1 (a closed or stained myocardium) than with TMPG 2 or 3 (open myocardium, median 13% versus 7%, P=0.004). Infarcts were also larger in patients with no ST segment resolution (median 15%) or incomplete resolution (11%) than in those with complete resolution (6%), overall P=0.0001. The difference in infarct size by TMPG persisted when stratified by category of ST resolution.

Conclusions—There may be a pathophysiological link between early restoration of tissue-level perfusion and reduced subsequent infarct size that may partially explain why these early angiographic and electrocardiographic measures are associated with long-term survival. (Circulation. 2002;105:282-285.)

Key Words: myocardial infarction ■ microcirculation ■ electrocardiography ■ angiography ■ thrombolysis

Current treatment of acute myocardial infarction (AMI) focuses on restoring epicardial blood flow.1,2 Even when epicardial flow is restored, however, the 30-day mortality rate may be 7-fold higher in patients with abnormal microvascular flow compared with those with normal microvascular flow.3 New therapies that may improve microvascular flow are being developed, as are techniques to measure it.4-7 These measurements, along with traditional estimates of infarct size, are associated with mortality after AMI.3,8-12 However, their relationships to each other are not well established, particularly the relationship between early angiographic and ECG measures and subsequent infarct size. We hypothesized that early abnormalities in perfusion would be associated with larger infarct size in the recent LIMIT AMI trial (Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction).13

Methods

The LIMIT AMI trial of rhuMAb CD18, a leukocyte adhesion inhibitor, was a randomized, double-blind, placebo-controlled study that enrolled 394 subjects in 60 centers in the United States and Canada between September 1998 and March 2000.13 Patients presenting within 12 hours of chest pain ≥ 30 minutes in duration and ST segment elevation on ECG were included. One of 2 doses of rhuMAb CD18 or placebo was administered before tissue plasminogen activator (tPA) or as soon as possible thereafter, along with aspirin and heparin. Because there were no differences in the effect of rhuMAb CD18 and placebo on trial endpoints, treatment groups were pooled in the present study. Percutaneous coronary intervention after 90-minute angiography and the use of other medications were at the discretion of the treating physician.

Angiographic and Electrocardiographic Assessment

TIMI flow grade1 and corrected TIMI frame count (CTFC)2 were measured at the TIMI Angiographic Core Laboratory from the
angiogram obtained 90 minutes after tPA. The TIMI myocardial perfusion grade (TMPG) was used to assess the tissue level perfusion in 247 patients (99.6% of consecutive patients; TMPG was added as an endpoint after the first 142 patients). The TMPG was previously defined as grade 0 (no angiographic blush), 1 (angiographic stain), 2 (dye bright at the end of injection, gone by next injection), and 3 (normal ground glass appearance).3 In 360 patients, standard ECGs were obtained 90 minutes after tPA. At a core laboratory blinded to all clinical data, the sum of ST segment elevation 20 ms after the J point was calculated and compared with the baseline ECG. The percent resolution was categorized as complete (>70%), partial (30% to <70%), or none (<30%).10

Infarct Size Assessment
Among 247 patients with a TMPG available, total creatine kinase release (myocardial band fraction, CK-MB) was reported as gram equivalents in 242 from measurements at 6, 12, 24, 48, and 72 hours after the administration of the study drug. In addition, 221 patients had infarct size determined by Technetium-99 m Sestamibi single photon emission computed tomography (SPECT) 120 hours after the administration of the study drug. At the nuclear core laboratory, the proportion of the left ventricle with a perfusion deficit was measured.12 Among 360 patients with interpretable ST segments, CK-MB release was determined in 352 and 320 had SPECT. The measures were highly correlated; with each gram equivalent increase in CK-MB, SPECT infarct size increased by 0.5% (Figure 1).

Statistical Analysis
Infarct size by CK-MB and SPECT were compared with the Kruskal-Wallis rank-sum test. To assess the consistency of TMPG and ST resolution in predicting infarct size, we tested for interactions with TIMI flow grade, infarct artery location, and lesion location (proximal or distal; significant \( P<0.01 \)), and we performed simple linear regression controlling for left ventricular ejection fraction (LVEF) on the 90-minute angiogram (as a crude early measure of infarct size). All analyses were performed with Stata version 7.0 (Stata Corporation).

Results
Infarcts determined by SPECT were larger with TMPG 0 and TMPG 1 than with TMPG 2 and TMPG 3 (Table 1). This pattern was also evident when comparing combined TMPG 0 to 1 (closed or stained myocardium) with combined TMPG 2 to 3 (open myocardium, Figure 2A). Similarly, as measured by CK-MB, larger infarcts occurred with TMPG 0 (median 15 grams, interquartile range 7 to 31) and TMPG 1 (13 grams, 9 to 18) than with TMPG 2 (10 grams, 5 to 13) and TMPG 3 (8 grams, 0 to 18, overall \( P=0.02 \)). Larger SPECT infarct sizes were also seen in patients with no or incomplete ST segment resolution than in those with complete ST segment resolution (Table 1, Figure 2B). Infarct size determined by CK-MB was larger in patients with no ST segment resolution (16 grams, 9 to 30) than with incomplete (10 grams, 5 to 28)

![Figure 1. Infarct size by SPECT (y-axis) versus CK-MB (x-axis).](image1)

![Figure 2. Cumulative distribution of infarct size by TMPG. These cumulative distributions show the infarct size for each patient by SPECT, stratified by TMPG (A) and category of ST segment resolution (B). The percentage of those patients with infarct size less than the value on the x-axis is shown on the y-axis. Small infarcts were more common among patients with TMPG 2 to 3 than with TMPG 0 to 1 \( P=0.004 \), and with complete ST resolution than with partial or no resolution \( P=0.0001 \).](image2)
TABLE 2. Association Between TIMI Myocardial Perfusion Grade (TMPG) and Infarct Size, Stratified by ST Segment Resolution

<table>
<thead>
<tr>
<th>Median SPECT Infarct Size, % LV (25, 75)</th>
<th>TMPG 0–1</th>
<th>TMPG 2–3</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>13 (5, 27)</td>
<td>7 (0, 18)</td>
<td>0.004</td>
</tr>
<tr>
<td>ST Resolution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30%, n=80</td>
<td>18 (5, 37)</td>
<td>13 (0, 26)</td>
<td>0.23</td>
</tr>
<tr>
<td>30%–69%, n=54</td>
<td>12 (0, 27)</td>
<td>8 (2, 20)</td>
<td>0.83</td>
</tr>
<tr>
<td>≥70%, n=75</td>
<td>11 (7, 16)</td>
<td>3 (0, 13)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

and complete ST segment resolution (10 grams, 3 to 18, overall P=0.0004).

There were no significant interactions with TIMI flow grade, infarct artery location, or lesion location. The differences in infarct size by TMPG and ST resolution were consistent across these strata. In particular, the trend was evident when restricted to TIMI 3 flow (Table 1). Larger LVEF at the 90-minute angiogram was associated with smaller SPECT infarct size (coefficient −0.3 per 1% increase in LVEF). However, when controlling for LVEF, both TMPG 2 to 3 (versus TMPG 1 to 2, coefficient −4.6, P=0.08) and complete ST segment resolution (versus no or incomplete resolution, coefficient −6.9, P=0.003) were associated with smaller SPECT infarct size. In each of the 3 categories of ST resolution, infarcts were larger in patients with TMPG 0 to 1 than with TMPG 2 to 3 (Table 2), and this pattern was consistent across categories of ST resolution (P=0.67 for interaction term).

Stratified by symptom-onset–to–treatment time (0 to 2, >2 to 4, >4 hours), presence of TMPG 2 to 3 (54%, 45%, 55%, P=0.3) and median CK-MB (12, 13, 13 grams, P=0.9) did not vary significantly. There was a trend toward more complete ST resolution (38%, 35%, 26%, P=0.26), and lower median SPECT (53%, 13%, 13%, P=0.11) with earlier treatment. There was a trend toward higher mortality with TMPG 0 to 1 than with TMPG 2 to 3 (4.9% versus 3.2%, P=0.05), and with no ST resolution versus partial or complete resolution (8.7% versus 2.0% and 4.2%, P=0.06).

Discussion
Several indices of perfusion after AMI have been associated with survival. Our study shows that early abnormalities in perfusion predict larger subsequent infarcts, a pattern observed with different measures of both perfusion (TMPG and ST segment resolution) and infarct size (CK-MB and SPECT).

These findings provide insight into the pathophysiology of early tissue perfusion and later infarct size. When abnormal microvascular flow was present, infarcts were larger, even after stratifying by other factors expected to affect infarct size. Both angiographic and ECG measures of perfusion were independently associated with subsequent infarct size, suggesting a potential electromechanical dissociation between microvascular blood flow and myocyte function. Although the angiogram may reflect mechanical patency of the microvasculature and the integrity of the endothelium, the ECG may reflect the functional status of the supplied myocardium. These data indicate that measurements of both processes are independent and complementary in their prognostic significance.

It is not clear whether larger infarcts impair early microvascular flow or, conversely, whether early perfusion abnormalities lead to subsequent increases in infarct size. Because the present data are observational in nature, the answer cannot be determined conclusively. Indeed, both phenomena may occur simultaneously in a cycle of worsening cell death. It is notable that after controlling for early LVEF, a crude estimate of early infarct size, both TMPG and ST resolution seemed to provide additional prognostic information with respect to later infarct size.

Limitations
The data were obtained from a randomized trial and the findings may not apply to patients in the general population. The TMPG data were available in a subset of all LIMIT AMI patients, but the baseline characteristics and outcomes in this cohort were similar to the cohort not studied (data not shown). Because the trial was relatively small, it lacks adequate statistical power to examine relationships between the clinical endpoints and mortality and to compare within subgroups of patients.

Conclusions
After thrombolytic therapy, early impairments in perfusion assessed by both TMPG and ST segment resolution are independently associated with larger subsequent infarct size on SPECT imaging. There may be a pathophysiological link between early restoration of tissue-level perfusion and reduced subsequent infarct size that may partially explain why these early angiographic and electrocardiographic measures are associated with long-term survival.

Acknowledgments
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