ST-Segment Recovery Adds to the Assessment of TIMI 2 and 3 Flow in Predicting Infarct Wall Motion After Thrombolytic Therapy

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Background—Early resolution of ST-segment elevation (ST-segment recovery) is associated with an improved outcome after infarction. Whether this relation is present in patients with Thrombolysis In Myocardial Infarction (TIMI) grade 2 or 3 flow (ie, patent) infarct-related arteries is not known.

Methods and Results—To examine the associations between time to achieve stable 50% ST-segment recovery assessed by continuous ECG monitoring, infarct artery flow, and infarct zone wall motion (at 48 hours), we studied 134 patients who underwent angiography at 99 (interquartile range 92 to 110) minutes after commencing streptokinase, initiated within 12 hours of onset of symptoms of myocardial infarction. Patients with TIMI 2 or 3 flow who failed to achieve early stable ST-segment recovery (50% ST-segment recovery sustained for 4 hours with <100 μV change in the peak lead) by 60 or 90 minutes had a higher fraction of chords in the infarct zone 2 SD below normal wall motion (TIMI 2: 55.5% vs 15.3%, P=0.006; and 56.5% vs 26.8%, P=0.01, respectively; and TIMI 3: 48.8% vs 28.3%, P=0.07; and 51.8% vs 29.9%, P=0.03, respectively). Time to stable ST-segment recovery was a multivariate predictor of infarct zone wall motion (P=0.04) independent of TIMI flow grade and the time from symptom onset to streptokinase therapy.

Conclusions—In patients with TIMI 2 or 3 flow in infarct-related artery, early stable ST-segment recovery is associated with improved infarct zone wall motion at 48 hours. ST-segment recovery may provide additional information about the degree of myocyte reperfusion achieved in patients with a patent epicardial infarct-related artery after thrombolytic therapy. (Circulation. 2000;101:2138-2143.)

Key Words: myocardial infarction ■ thrombolysis ■ reperfusion ■ myocytes ■ streptokinase

An optimal outcome after thrombolytic therapy for acute myocardial infarction depends on complete and sustained reperfusion of the infarct-related artery.1,2 Patients with angiographically assessed Thrombolysis In Myocardial Infarction (TIMI) grade 3 (normal) flow in the infarct-related artery 90 minutes after commencement of thrombolytic therapy have more favorable early and medium-term outcomes compared with patients with TIMI 0 to 2 (absent or reduced) flow.3,4

Angiographic examination of epicardial infarct artery flow is undertaken over a constrained time period, and cannot provide continuous assessment or determine the degree of perfusion at the myocyte level. Early resolution of ST-segment elevation (ST-segment recovery) on the ECG has frequently been used to noninvasively predict infarct artery patency (TIMI 2 or 3 flow).5,6 However, it is known that a patent epicardial infarct artery does not necessarily result in reperfusion at the cellular level,7,8 and it has been suggested that ST-segment recovery may be a better marker of myocyte reperfusion, and consequently of clinical outcome.9

In this study, we determined whether early stable 50% ST-segment recovery, assessed by continuous ECG ST-segment monitoring, was an independent predictor of infarct zone wall motion at 48 hours in patients with TIMI 2 or 3 flow in the infarct-related artery at a median of 99 minutes after the institution of thrombolytic therapy for acute myocardial infarction.

Methods

Patients
Patients with acute myocardial infarction randomized in the Hirulog Early Reperfusion Occlusion (HERO-1) trial,10 who underwent continuous ST-segment monitoring, early coronary angiography, and ventriculography at 48 hours after streptokinase infusion, formed the study group. Patients were eligible for randomization in HERO-1 if

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they presented to hospital with a history of chest pain lasting >20 minutes within the preceding 12 hours, and had ≥1 mm of ST-segment elevation in 2 contiguous leads (or ≥2 mm in leads V5 through V6) on the ECG.10

**Treatment Regimen**

All patients received 150 to 325 mg aspirin and 1.5×10^6 U of streptokinase ever a period of 30 to 60 minutes, and were randomized to receive either heparin (5000-U bolus followed by 1000 to 1200 U/h titrated to a therapeutic activated partial thromboplastin time) or one of two doses of bivalirudin (previously known as hirulog). The low-dose bivalirudin group received a 0.125-mg bolus followed by 0.25 mg · kg\(^{-1}\) · h\(^{-1}\), and the high-dose bivalirudin group received double these doses.

**Cardiac Catheterization**

The HERO-1 protocol recommended coronary angiography at 90 to 120 minutes after the start of streptokinase therapy, and at 48 hours in conjunction with ventriculography.10 TIMI flow grades11 and corrected TIMI frame counts12,13 were assessed by 2 experienced analysts blinded to clinical outcomes. If flow grades differed between the 2, a third independent observer adjudicated. The presence or absence of a collateral circulation was determined through the use of the Rentrop grading system.14 Ventriculography was performed in the 40° right anterior oblique projection and analyzed separately by the Cardiovascular Measurement System (CMS-Medis Medical Imaging Systems, Nuenen, The Netherlands) for regional wall-motion analysis. Infarct zone wall motion was assessed through the use of the centerline method,13,15 and regional motion parameters were expressed as either the mean chord motion or the fraction of chords with motion >2 SD below normal.

**Continuous ST-Segment Monitoring**

Twelve-lead continuous ECG ST-segment monitoring was performed with the use of a Mortara ST-100 monitor for 24 hours, commencing immediately before the streptokinase infusion. The traces were analyzed at Duke University, Durham, North Carolina, as previously described.10 The prespecified primary end point was the time to stable ST-segment recovery, defined as the time from initiation of thrombolytic therapy to the first ECG recording showing sustained 50% resolution from a preceding peak ST level. Recovery was assumed to be sustained if it persisted for ≥4 hours with <100-μV change in the peak lead. In addition to continuous variable analysis, we also assessed the effect of stable ST-segment recovery on infarct zone wall motion at 45, 60, and 90 minutes. The time to initial 50% ST-segment recovery (ie, the time to the first 50% reduction in ST-segment elevation) was a secondary end point.

**Statistical Analysis**

Results for continuous variables are expressed as mean±SD, and differences were compared by means of a paired or unpaired t test. Categorical variables are expressed in percentages, with comparisons made with the use of a χ² or Fisher’s exact test. Multivariate analysis was performed with the use of forward stepwise linear regression to identify independent predictors of infarct zone wall motion. All variables with a probability value of <0.05 were initially entered into a multivariate model. Variables with the highest probability values were removed sequentially until the model with the most powerful probability value was achieved. A 2-tailed probability value of <0.05 was regarded as significant.

**Results**

Of the 412 patients enrolled in the HERO-1 trial,10 210 patients underwent ST-segment monitoring, and 172 (82%) had recordings suitable for analysis. Stable ST-segment recovery was achieved during the monitoring period by 163 patients, and 134 had angiographic data and ventriculograms suitable for wall motion analyses. Coronary angiography was performed at a median of 99 (interquartile range 92 to 110) minutes after the institution of streptokinase therapy, and 37 (28%) had TIMI 0 to 1 flow, 40 (30%) TIMI 2 flow, and 57 (42%) TIMI 3 flow. There were no differences in baseline characteristics between these 134 patients, the 210 patients with ST-segment monitoring, and the total HERO-1 cohort of 412 patients (Table 1).

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HERO-1</th>
<th>Patients with ST Monitoring†</th>
<th>Patients With Complete Data Sets‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>412</td>
<td>210</td>
<td>134</td>
</tr>
<tr>
<td>Age, y*</td>
<td>61.4±12</td>
<td>61.7±12</td>
<td>61.1±11</td>
</tr>
<tr>
<td>Female, %</td>
<td>25</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>14</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Prior angioplasty, %</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Prior coronary bypass surgery, %</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>30</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>63</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Time from symptom onset to therapy, h*</td>
<td>3.9±2.7</td>
<td>4.1±2.6</td>
<td>4.0±2.6</td>
</tr>
<tr>
<td>Duration of streptokinase infusion, min*</td>
<td>50±16</td>
<td>50.4±17</td>
<td>49.1±18</td>
</tr>
<tr>
<td>Bivalirudin treatment, %</td>
<td>66</td>
<td>68</td>
<td>66</td>
</tr>
</tbody>
</table>

*Mean±SD.
†All patients from the HERO-1 study who underwent continuous ST-segment monitoring.
‡All patients with suitable angiographic and ECG data from the continuous ST-segment monitoring subgroup.

Of the 134 patients, 22 (17%) achieved stable ST-segment recovery by 45 minutes, 26 (20%) by 60 minutes, and 40 (30%) by 90 minutes. In patients with TIMI 3 flow, 11 (19%) achieved stable recovery by 45 minutes, 14 (25%) by 60 minutes, and 21 (37%) by 90 minutes. In patients with TIMI 2 flow, 6 (15%) achieved stable recovery by 45 minutes, 7 (18%) by 60 minutes, and 12 (30%) by 90 minutes. In patients with TIMI 0 to 1 flow, 4 (11%) achieved stable recovery by
Infarct zone wall motion, ST-segment recovery, and TIMI flow grades. The mean infarct zone chord score in patients who achieved or did not achieve 50% stable ST-segment recovery by 45, 60, and 90 minutes after commencement of thrombolytic therapy is shown. Results are shown for all patients and for those with TIMI 0 to 1, 2, or 3 flow in the infarct artery at 90 minutes. A, Mean infarct zone chord score; B, frequency of infarct zone chords >2 SD below normal motion.

45 minutes, 4 (11%) by 60 minutes, and 6 (16%) by 90 minutes. Among all patients with TIMI 2 or 3 flow, there was a correlation between the time to stable ST-segment recovery and the corrected TIMI frame count, assessed as continuous variables (r=0.26; P=0.003). There was no relation between CTFC and initial 50% ST-segment recovery.

In the overall study group, failure to achieve early stable ST-segment recovery was associated with a lower mean chord score and a higher fraction of chords >2 SD below normal in the infarct zone at all times from 45 to 90 minutes (Figure). Patients with either TIMI 2 or 3 flow who failed to achieve early stable ST-segment recovery also had a lower mean chord score and a higher fraction of chords >2 SD below normal wall motion in the infarct zone (Figure). Among the 97 patients with TIMI 2 or 3 flow, those who achieved stable ST-segment recovery had fewer chords >2 SD below normal motion and a higher mean chord score in the infarct zone at 45 minutes (19.2% vs 50.9%), P<0.0001; and −1.28 vs −2.49, P=0.002; respectively), at 60 minutes (24.0% vs 51.2%, P=0.0004; and −1.49 vs −2.49, P=0.003; respectively) and at 90 minutes (28.8% vs 53.9%, P=0.0005; and −1.72 vs −2.56, P=0.006; respectively).

In patients with TIMI 0 to 1 flow, failure to achieve early stable ST-segment recovery appeared to have no effect on regional wall motion (Figure). However, only 4 patients with TIMI 0 to 1 flow achieved stable ST-segment recovery by 45 or 60 minutes, and 6 patients by 90 minutes. We investigated whether the presence of a collateral circulation affected time to ST-segment recovery, particularly in the TIMI 0 to 1 subgroup. The mean time to stable ST-segment recovery in 13 patients with TIMI 0 to 1 flow and Rentrop grade 2 or 3 collaterals was 269±410 minutes compared with 240±230 minutes in 24 patients with Rentrop grades 0 or 1 (P=0.8).

There was no difference in the median time to stable ST-segment recovery between the heparin, low-dose bivalirudin and high-dose bivalirudin treatment groups (126 vs 112 vs 118 minutes, respectively, P=0.50), and between the heparin and both bivalirudin groups combined (126 vs 118 minutes, P=0.46).

TABLE 2. Early Stable ST Recovery in Patients With TIMI 0 to 1 Flow: Effect of Collateral Circulation

<table>
<thead>
<tr>
<th>Grade 0 to 1 Collaterals</th>
<th>Grade 2 to 3 Collaterals</th>
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<tbody>
<tr>
<td>No. of Patients</td>
<td>No. of Patients</td>
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</table>

<table>
<thead>
<tr>
<th>Stable ST recovery by 45 min?</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>No. of Patients</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Stable ST recovery by 60 min?</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>No. of Patients</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Stable ST recovery by 90 min?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

Univariate and Multivariate Predictors of Infarct Zone Wall Motion

Univariate analysis was performed on clinical baseline characteristics, times to both stable and initial ST-segment recovery, and angiographic flow grades in order to identify variables that might predict infarct zone wall motion (Table 3). On multivariate analysis, there were 2 variables that independently predicted infarct zone wall motion: time to stable ST-segment recovery (P=0.044), and time to initial ST-segment recovery (P=0.045).

Discussion

The major finding of this study is that early stable ST-segment recovery in patients with a patent infarct artery (both TIMI 2 and TIMI 3 flow) after thrombolytic therapy for acute myocardial infarction is associated with improved infarct zone wall motion at 48 hours. On multivariate analysis, time to stable ST-segment recovery was an independent predictor of infarct zone wall motion, whereas TIMI flow grade and the
angioplasty, the degree of ST-segment recovery at 60 minutes achieved TIMI 3 flow in the infarct artery after primary reperfusion. In a study of patients who conventionally would have been classified as having had TIMI 3 flow in the epicardial infarct-related artery, who had TIMI 3 flow in the epicardial infarct-related artery, myocyte perfusion and presumably microvascular flow have been achieved in some patients. Thus initial and stable ST-segment recovery, determined by continuous monitoring, may partly reflect restoration of both infarct artery flow and microvascular flow.

Timing and Amount of ST-Segment Recovery

Although the degree of ST-segment recovery required to identify reperfusion on the postthrombolytic ECG remains contentious, 50% ST-segment recovery has been proposed by several authors. The ideal time to assess ST-segment recovery is unclear. Recording the time to stable ST-segment recovery (instead of time to initial ST-segment recovery) ensures that the early ST-segment fluctuations that are demonstrated by 35% to 50% of patients during reperfusion are not misinterpreted as permanent resolution of ST-segment elevation. Unlike “snapshot” ECGs, continuous ST-segment monitoring allows this phenomenon to be accurately monitored after thrombolytic therapy, but requires greater input from medical and nursing staff. Technical difficulties can also occur. Indeed, only 82% of patients in this substudy of HERO-1, which was performed in several coronary care units, had recordings suitable for analysis.

An occluded infarct-related artery (TIMI 0 or 1 flow) at early angiography represents a “snapshot” of infarct artery flow, and ST-segment recovery may have occurred either because the artery was “mainly open” or because the myocardium in the infarct zone was supplied by collaterals too small to be detected angiographically. There was no association between earlier stable ST-segment recovery and improved infarct zone wall motion in patients with TIMI 0 to 1 flow. However, the small number of patients achieving early stable ST-segment recovery in this subgroup rendered the detection of a statistically significant difference unlikely. Perhaps for the same reason, no association was found between the presence of collateral circulation on the early angiogram and early stable ST-segment recovery. Whether collateral blood flow influences the time to ST-segment recovery requires further prospective evaluation.

Study Limitations

This study has several potential limitations. Although the patients enrolled in the HERO-1 trial who underwent continuous ST-segment monitoring had baseline characteristics similar to those who did not undergo monitoring, a selection bias could have occurred. TIMI flow assessments were made at 99 (interquartile range 92 to 110) minutes, and may have differed at 45, 60, or 90 minutes, when ST-segment recovery was assessed. Ventricular function was measured at 48 hours, at which stage some of the ventricular dysfunction observed could have been due to myocardial stunning. In addition, the patients who died or underwent revascularization before the recommended 48-hour ventriculogram would most likely have been found to have impaired ventricular

<table>
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<th>Variable</th>
<th>P</th>
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<tr>
<td>Sex</td>
<td>0.92</td>
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<tr>
<td>Age</td>
<td>0.74</td>
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<tr>
<td>TIMI flow grade*</td>
<td>0.41</td>
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<tr>
<td>Corrected TIMI frame count†</td>
<td>0.85</td>
</tr>
<tr>
<td>Time to initial 50% ST recovery</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to stable 50% ST recovery</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.36</td>
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<tr>
<td>Heparin vs low-dose vs high-dose hirulog</td>
<td>0.20</td>
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<tr>
<td>Previous infarction</td>
<td>0.29</td>
</tr>
<tr>
<td>Previous angioplasty</td>
<td>0.24</td>
</tr>
<tr>
<td>Previous coronary bypass surgery</td>
<td>0.75</td>
</tr>
<tr>
<td>Symptom onset to streptokinase time</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*TIMI 2 and 3 vs TIMI 0 to 1; P=0.52.
†Corrected TIMI frame count as a continuous variable.

When corrected TIMI frame count was included as a dichotomous variable (<40 vs ≥40), P=0.15.

time from symptom onset to initiation of streptokinase therapy were not.

Coronary angiography has been regarded as the method of choice for assessing success of reperfusion therapy, and patency of the infarct artery is an established prognostic indicator after infarction, but as a “gold standard” investigation, angiography has its limitations. Infarct artery flow after thrombolytic therapy is a dynamic process, and the “snapshots” in time provided by coronary angiography may not accurately represent flow within the infarct-related artery during the early hours after the administration of reperfusion therapy. Even if the artery is patent at angiography, this does not necessarily signify reperfusion at the myocyte level. Myocardial contrast echocardiographic studies have confirmed that a significant proportion of patients who achieve TIMI 3 flow in the infarct-related artery continue to have poor tissue perfusion or “no reflow.” Other studies have suggested that myocardial perfusion imaging techniques such as positron emission tomography and MRI may aid in the identification of nonreperfused myocytes.

In this study, we have demonstrated that early stable 50% ST-segment recovery, assessed by continuous ST-segment monitoring, is associated with improved infarct zone wall motion at 48 hours after myocardial infarction in patients with patent epicardial infarct-related arteries, regardless of angiographic flow, assessed either by TIMI flow grading or corrected TIMI frame counting. The corrected TIMI frame count at 99 minutes (the median time of angiographic assessment) correlated with the time to stable ST-segment recovery. Early, stable ST-segment recovery predicted better preservation of regional ventricular function in patients who had TIMI 3 flow in the epicardial infarct-related artery, who conventionally would have been classified as having achieved successful reperfusion. In a study of patients who achieved TIMI 3 flow in the infarct artery after primary angioplasty, the degree of ST-segment recovery at 60 minutes was an independent predictor of mortality during a 3-year follow-up period. We also found that measurement of ST-segment recovery added to the assessment of TIMI-2 flow in predicting infarct zone wall motion. This suggests that despite the reduction in infarct artery epicardial blood flow, myocyte perfusion and presumably microvascular flow have been achieved in some patients. Thus initial and stable ST-segment recovery, determined by continuous monitoring, may partly reflect restoration of both infarct artery flow and microvascular flow.
function. Thus the association between ST-segment recovery and infarct zone wall motion at 90 minutes in patients with TIMI 2 or 3 flow might have been more powerful if these patients had been able to be evaluated. In our earlier report of 251 patients from HERO-1,13 the relation between infarct artery flow, assessed as corrected TIMI frame counts (<40 vs ≥40), and 48-hour infarct zone wall motion had a probability value of 0.025, whereas in the current data set, which also required patients to have ST-segment monitoring suitable for analysis, the probability value was 0.15, reflecting a decrease in study power. Finally, the study lacked the statistical power to demonstrate differences in clinical outcomes.

Clinical Implications
We have shown that failure to achieve early ST-segment recovery after thrombolytic therapy is associated with impaired ventricular function.25 Thus, patients at increased risk of ventricular dysfunction may be identified early after thrombolytic therapy through the use of continuous ST-segment monitoring. Trials are required to test adjunctive therapies with agents such as verapamil,26 potassium ATP channel openers such as nicorandil,27 or adenosine,28 which may limit the amount of microvascular damage in the setting of failed myocyte perfusion. Evidence from the TIMI 14 Study29 shows that abciximab improves epicardial coronary artery blood flow. Patients who had a patent infarct-related artery 60 minutes after the commencement of abciximab and thrombolytic therapy had a higher frequency of >70% ST-segment resolution at 90 minutes.30 This suggests that abciximab may also improve microvascular flow, and consequently myocyte perfusion, by reducing platelet aggregates and platelet emboli.

Conclusions
With the use of continuous monitoring, early stable ST-segment recovery is associated with less abnormal infarct zone wall motion at 48 hours after thrombolytic therapy in patients with TIMI 2 or 3 flow. ST-segment recovery may therefore provide information about the degree of myocyte reperfusion, and thus microvascular flow, achieved in patients with a patent epicardial infarct artery after myocardial infarction. This may allow identification of patients at higher risk who may be considered for additional treatments. Such strategies require formal evaluation in future studies.

Acknowledgments
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References


22. Purcell IF, Newall N, Farrer M. Change in ST segment elevation 60 minutes after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes. *Heart*. 1997;78:465–471.


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