Early T Wave Inversion After Thrombolytic Therapy Predicts Better Coronary Perfusion: Clinical and Angiographic Study

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Objectives. This study was undertaken to test the hypothesis that early inversion of T waves after thrombolytic therapy for acute myocardial infarction predicts patency of the infarct-related artery with high Thrombolysis in Myocardial Infarction (TIMI) perfusion flow and better in-hospital outcome.

Background. Although numerous studies have demonstrated a strong association between early resolution of ST segment elevation after acute myocardial infarction and successful thrombolysis, little is known about early changes in T waves after thrombolytic therapy.

Methods. Ninety-four consecutive patients with acute myocardial infarction treated with recombinant tissue-type plasminogen activator (rt-PA) were studied with admission and predischARGE radiolucent ventriculography and with coronary angiography within 72 h of admission. Patient stratification was based on the presence or absence of early (within 24 h) T wave inversion.

Results. Early T wave inversion was associated with a higher rate of the infarct-related artery (90% vs. 65%, p < 0.02) and less severe residual stenosis ([mean ± SD] 73 ± 27 vs. 83 ± 22, p = 0.06), and when only TIMI perfusion grade 3 was considered, the difference was even greater (77% vs. 45%, p < 0.001). Patients with early inversion of T waves had a lower peak creatine kinase value ([mean ± SD] 678 ± 480 vs. 1,076 ± 620, p < 0.01), and although a similar percent of patients with and without early T wave inversion had a normal ejection fraction (≥55%) on admission, a higher percent of patients with early inversion had a normal ejection fraction at hospital discharge (71% vs. 44%, p < 0.05). Early T wave inversion anticipated a more benign in-hospital clinical course with a lower incidence of adverse cardiac events (18% vs. 33%, p < 0.02).

Conclusions. Early inversion of T waves in patients with acute myocardial infarction treated with thrombolytic therapy suggests patency of the infarct-related artery, better perfusion grade and left ventricular function, and a more benign in-hospital course.

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Successful thrombolytic therapy is associated with rapid resolution of ST segment elevation (1-17) and in a substantial portion of patients is followed by the early and rapid appearance of new pathologic Q waves and R wave amplitude loss (4,6,11,16-19). Although a great deal of attention has been paid to the significance of early changes in the ST segment after thrombolytic therapy (1-17), little attention has been paid to early changes in the T wave (20). In this study, we evaluated the relation of early T wave inversion occurring within the 1st 24 h of recombinant tissue-type plasminogen activator (rt-PA) administration to the clinical outcome in patients with acute myocardial infarction. Our results suggest that early T wave inversion after administration of thrombolytic therapy is a marker of a better in-hospital course, indicating therefore a successful and effective thrombolytic treatment.

Methods

Study patients. The study group included 94 consecutive patients with acute myocardial infarction who received intravenous rt-PA as a part of the research protocol. Eligible for the study were patients <75 years old with ischemic pain of at least 30 min in duration but not >4 h and ST segment elevation of at least 1 mm in two or more contiguous electrocardiographic (ECG) leads.

Excluded from the study were patients with complete left bundle branch block on admission ECG or with one of the following contraindications to thrombolytic therapy: history of bleeding diathesis, recent (<6 months) cerebrovascular accident, active peptic disease, recent (<6 weeks) surgery or trauma or severe hypertension (>180 mm Hg systolic or >120 mm Hg diastolic blood pressure). None of the patients had a revascularization procedure before the qualifying myocardial infarction.

Thrombolytic protocol. All patients were treated with 120 mg of rt-PA administered intravenously over 6 h. Imme-
diately before the initiation of rt-PA therapy, an intravenous bolus of 5,000 IU of heparin was administered, followed by continuous infusion of 1,000 IU/h for at least 5 days. Aspirin was given in a daily dose of 250 mg starting on the second day. Blood samples were obtained every 3 h during the 1st 24 h and once daily from the second day for determination of total serum creatine kinase (CK) activity and MB isoenzyme (CK-MB) fraction.

Electrocardiography. A 12-lead ECG was recorded on admission and every 3 h thereafter during the 1st 24 h after admission. Beyond the 1st 24 h, a 12-lead ECG was recorded daily throughout the hospital stay. All ECGs were recorded with identical (marked) positions of the chest leads. Analysis of the ECGs was performed by two independent investigators who had knowledge of neither the results of the other investigations nor the clinical data.

The 24-h ECG was reviewed for the presence of T wave inversion in at least half of the same leads in which initial ST segment elevation was observed on the admission ECG. The T wave was considered inverted if it was monophasic negative and its amplitude was ≥1 mm.

Two groups of patients were identified according to the changes in T waves in the 24-h ECGs: patients who had patients without inversion of T waves.

In a preliminary ECG analysis, we also examined the predictive value of T wave inversion in the 3- and the 12-h ECG. We report here only the results from the analysis of the 24-h ECG because T wave inversion in this ECG was found to be the best predictor of patency and clinical outcome.

Coronary angiography. Each patient underwent coronary angiography within 72 h of the initiation of rt-PA infusion. Coronary angiograms were reviewed by two independent observers who were unaware of other clinical data except for the ECG infarct location.

The infarct-related artery was considered patent if coronary flow was scored as Thrombolysis in Myocardial Infarction (TIMI) perfusion grade 2 or 3 (21). The percent diameter stenosis of the infarct-related artery was quantitatively calculated by comparing the narrowest diameter of the stenosis in both right and left anterior oblique projections to the normal adjacent diameter of the artery.

Percutaneous transluminal coronary angioplasty of the infarct-related lesion was attempted in all patients with suitable coronary anatomy, irrespective of their clinical status, as part of the research protocol.

Radionuclide ventriculography. Each patient underwent two rest radionuclide ventriculographic studies throughout the hospital stay: the first as early as possible after entering the study, but no later than 24 h, and the second at discharge. Each examination was reviewed by two experienced cardiologists who had no knowledge of the patient's other clinical data. A multigated equilibrium blood pool scan was performed in the anterior and 45° left anterior oblique projections. Left ventricular ejection fraction was calculated from the 45° left anterior oblique projection. Normal left ventricular function was defined as ejection fraction ≥55%.

Statistical analysis. For continuous variables the results are given as mean value ± SD, and the comparisons of the two groups were performed by standard t test. Changes in left ventricular ejection fraction between admission and predischarge radionuclide studies within each of the two groups were evaluated by the nonparametric paired t test. Frequencies of discrete variables were compared between the two groups using chi-square analysis with the Yates correction or Fisher exact test.

Results

The diagnosis of acute myocardial infarction was confirmed in all 94 patients by at least a twofold increase in CK level, with CK-MB isoenzyme fraction >5%. Of the 94 patients, 9 were excluded from analysis: 4 underwent emergency coronary angioplasty within the 1st 12 h, and 5 others developed right bundle branch block, which may by itself alter the configuration of T waves.

Of the 85 patients included in the analysis, 39 (46%) had T wave inversion within 24 h, and 46 (54%) did not. Baseline characteristics of the two groups of patients are presented in Table 1. The two groups were generally comparable. The incidence of anterior infarct was slightly higher (41% vs. 33%), and the mean interval lapse between onset of symptoms and initiation of rt-PA infusion was longer, in patients without than in those with early T wave inversion (145 ± 110 min vs. 118 ± 46 min, p = 0.13); however, these differences did not reach statistical significance.

Coronary angiography. Coronary angiography was performed in all 85 patients (Table 2). The number and distribution of diseased vessels did not differ significantly between the two study groups. The mean number of diseased coro-
Table 2. Findings During Coronary Angiography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 39)</th>
<th>Group B (n = 46)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to catheterization (days)</td>
<td>2.6 ± 1.1</td>
<td>2.8 ± 1.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Multivessel CAD (%)</td>
<td>46</td>
<td>37</td>
<td>0.14</td>
</tr>
<tr>
<td>No. of diseased coronary arteries</td>
<td>1.6 ± 0.8</td>
<td>1.5 ± 0.8</td>
<td>0.33</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patency (%)</td>
<td>90</td>
<td>65</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>TIMI grade 3 flow (%)</td>
<td>77</td>
<td>41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI perfusion grade</td>
<td>2.5 ± 0.95</td>
<td>2.0 ± 1.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Percent residual diameter stenosis</td>
<td>73 ± 20</td>
<td>83 ± 12</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or number or percent of patients. TIMI = Thrombolysis in Myocardial Infarction; other abbreviations as in Table 1.

Table 3. Findings During Coronary Angiography According to Infarct Site

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>13</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Multivessel CAD (%)</td>
<td>46</td>
<td>22</td>
<td>0.26</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Patency</td>
<td>100</td>
<td>58</td>
<td>0.03</td>
</tr>
<tr>
<td>TIMI grade 3 flow (%)</td>
<td>77</td>
<td>26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI perfusion grade</td>
<td>2.7 ± 0.5</td>
<td>1.8 ± 1.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent residual diameter stenosis</td>
<td>78 ± 15</td>
<td>90 ± 8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or number or percent of patients (pts). LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NCA = normal coronary artery; RCA = right coronary artery; other abbreviations as in Tables 1 and 2.

The infarct-related artery was patent in 65 (76%) of the 85 patients. The patency rate of the infarct-related artery was significantly higher among patients with early inversion of the T wave compared with patients without early inversion (90% vs. 65%, p = 0.02). When only TIMI 3 perfusion grade was considered, the difference was even greater (77% vs. 41% for patients with and without early T wave inversion, respectively, p < 0.001) (Fig. 1). Accordingly, although most (88%) patients with a patent infarct-related artery had TIMI perfusion grade 3, only 63% of those with a patent infarct-related artery but without early T wave inversion had TIMI 3 perfusion grade. In accordance, only among those patients with a patent infarct-related artery was the mean residual stenosis in the infarct-related artery less severe in patients with early T wave inversion (73 ± 20% vs. 83 ± 12%) than in patients without early T wave inversion (p = 0.06). Despite the relatively small number of patients with anterior infarction (32 patients), a highly significant difference in infarct-related artery patency was observed between patients with and without T wave inversion (100% vs. 58%, respectively, p = 0.03) (Table 3). Among all patients, the difference was even greater when the proportion of patients with only TIMI perfusion grade 3 was compared (77% vs. 28% for patients with and without early T wave inversion, respectively, p < 0.006) (Fig. 2), and the mean residual stenosis in the culprit vessel was somewhat less severe in these patients (78 ± 15% vs. 90 ± 8%, p = 0.03). Similar trends, although statistically insignificant, were observed in patients with inferior infarction (Table 3, Fig. 3).
Coronary angioplasty was performed in a comparable number of patients with and without early T wave inversion (46% vs. 49%, respectively, p = 0.97).

Enzymatic infarct size. Peak CK value was significantly lower in patients than patients without early T wave inversion (678 ± 480 vs. 1,076 ± 620, respectively, p < 0.01). A similar difference was observed among patients with anterior infarction with and without early T wave inversion (750 ± 610 vs. 1,242 ± 730, p < 0.05), whereas in patients with inferior infarction, only an insignificant trend toward lower peak CK was noted in patients with early T wave inversion (809 ± 602 vs. 1,246 ± 763, p = 0.08).

Radionuclide ventriculography. Admission and predischarge radionuclide ventriculographic studies were available in 76 (89%) and 80 (94%) patients, respectively. At admission, the rate of patients with a normal ejection fraction (≥55 units) was basically similar in patients with and without early T wave inversion (49% vs. 42%, p = 0.14). At discharge, however, a significantly higher proportion of the patients with early T wave inversion had normal left ventricular function compared with patients without (71% vs. 44%, p < 0.03). Among patients with anterior infarction, this difference was even greater (62% vs. 22%, p < 0.05).

Paired (admission and predischarge) radionuclide ventriculograms were available in 33 (85%) patients with and 40 (87%) patients without T wave inversion. Significant improvement in left ventricular ejection fraction was observed only in patients with early T wave inversion, with a mean increase of 7.2 ± 15 in ejection fraction units (p = 0.01), whereas in patients without T wave inversion, the mean change in left ventricular ejection fraction was an increase of only 3.1 ± 12 in ejection fraction units (p = 0.15). Similar findings were demonstrated when the significance of early inversion of T waves with regard to the left ventricular ejection fraction was considered separately among patients with anterior and inferior infarct. Early T wave inversion predicted significant left ventricular ejection fraction improvement throughout the hospital stay both in patients with anterior (9 ± 12, p < 0.05) and with inferior (6 ± 11, p < 0.04) infarct, whereas patients without early inversion of T waves did not significantly improve their ejection fraction during the hospital stay whether they had anterior (5 ± 13, p = 0.5) or inferior (−2 ± 10, p = 0.9) infarct.

In-hospital clinical course. None of the patients with early T wave inversion had clinical evidence of early (within the 1st 72 h) reinfarction, but nine (20%, p < 0.01) of the patients without early T wave inversion had early reinfarction (Table 4). Congestive heart failure and postinfarction angina were also more common among patients without early T wave inversion compared with patients with early T wave inversion (6.5% and 6.5% vs. 2.6% and 0%, respectively). On the whole, patients without early T wave inversion had a more complicated in-hospital course compared with those with early inversion of T waves. A significantly higher proportion of patients without early T wave inversion had at least one adverse cardiac event (including fatal and nonfatal reinfarction, postinfarction angina, overt congestive heart failure and cardiac death) throughout their hospital stay compared with patients with early T wave inversion (33% vs. 10%, p < 0.02).

Discussion

Successful reperfusion with thrombolytic therapy may accelerate ECG evolution of infarction (4,6,11,16-19). These studies postulated that rapid resolution of ST segment elevation followed by rapid development of pathologic Q waves and R wave loss are suggestive of successful reperfusion.
ity of the residual lesion (27-29) or the TIMI perfusion grade in the early T wave inversion group.

In contrast, is in addition to the benefit of a higher patency rate to the better ventricular function in these patients. This, of versus those without early T wave inversion may contribute among patients with a patent infarct-related artery. However, they found no relation between these rapid repolarization changes and left ventricular function. To our knowledge, no other published study evaluated the significance of early T wave inversion after thrombolytic therapy.

Our findings suggest that early (within 24 h) inversion of T waves after thrombolytic therapy is predictive of successful and effective reperfusion. Early T wave inversion was associated with more frequent and more adequate patency of the infarct-related artery. The higher patency with better perfusion of the infarct-related artery among patients with versus those without early inversion of T waves was accompanied by better myocardial preservation, as reflected by smaller enzymatic infarct size, substantial improvement of left ventricular ejection fraction throughout the hospital stay and better ventricular function at discharge. The TEAM-2 investigators (24) failed to demonstrate infarct size reduction after thrombolytic therapy in patients with TIMI grade 2 compared with significant infarct size limitation in patients with grade 3 flow. They therefore suggested that only TIMI grade 3 led to optimal myocardial salvage. This agrees with previous studies (25,26) that showed that high degree residual stenosis despite successful reperfusion of the infarct-related artery might interfere with recovery of the left ventricular function. Thus, the less severe residual stenosis and the lower rate of TIMI flow 2 in the infarct-related artery among patients with a patent infarct-related artery with versus those without early T wave inversion may contribute to the better ventricular function in these patients. This, of course, is in addition to the benefit of a higher patency rate in the early T wave inversion group.

Previous studies after reperfusion with thrombolytic therapy demonstrated a positive correlation between the severity of the residual lesion (27-29) or the TIMI perfusion grade (30) of the culprit vessel and the likelihood of recurrent angina or reinfarction, or both. Hence, the more severe residual stenosis and the higher rate of TIMI perfusion grade 2 among patients without early inversion of T waves may also account for the more complicated in-hospital course noted in those patients.

Early inversion of T waves in association with successful thrombolysis and salvage of jeopardized myocardium might be related to the special pattern of left ventricular innervation. The sympathetic nerve fibers to the left ventricle travel in the subepicardium in a basal–apical course along with the coronary arteries (31,32); therefore, any infarct results in denervation of the more apical myocardium (33-35). Usually, even successful thrombolysis cannot prevent some myocardial necrosis; thus, at least part of the salvaged myocardium distal to the area of necrosis in the apical region, although viable, is sympathetically denervated. Because sympathetic denervation delays repolarization (33-36), the ECG presentation of salvaged but denervated myocardium in the facing ECG leads would be early inversion of T waves, whereas in necrotic myocardium, where there is no electrical activity, the interruption in the innervation would not be expressed.

Clinical implications. Although early inversion of T waves was associated in the present study with a significantly higher patency rate of the infarct-related artery, absence of early inversion did not exclude patency of the infarct-related artery. However, even if reperfusion occurred among patients without early T wave inversion, a more severe residual stenosis and lower TIMI perfusion grade might be anticipated with less myocardial salvage and with a higher incidence of in-hospital complications, especially reinfarction. Thus, early inversion of T waves is not accounted for by any degree of reperfusion but requires for its occurrence adequate reperfusion, which results in significant myocardial perfusion and salvage. Therefore, patients without early T wave inversion must be monitored very carefully and designated for catheterization at any sign of recurrent ischemia.

The relatively small number of patients in this study calls for caution. However, the present study results do suggest a significantly more favorable in-hospital outcome in patients with early inversion of T waves. Thus, an early inversion of the T wave may indicate a physiologically successful reperfusion.

### Table 4. In-Hospital Clinical Outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>Group B</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinfarction</td>
<td>7.7</td>
<td>27</td>
</tr>
<tr>
<td>Early reinfarction (within 72 h)</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Late reinfarction</td>
<td>7.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Postinfarct angina</td>
<td>0</td>
<td>6.5</td>
</tr>
<tr>
<td>CHF at discharge</td>
<td>2.6</td>
<td>6.5</td>
</tr>
<tr>
<td>Death</td>
<td>5.0</td>
<td>6.5</td>
</tr>
<tr>
<td>At least one of adverse cardiac event</td>
<td>10</td>
<td>33</td>
</tr>
</tbody>
</table>

Data presented are percent of patients. CHF = congestive heart failure.

These clinical observations are supported by previous experimental studies in canine models (22,23), where an accelerated appearance of pathologic new Q waves was noted immediately after the release of coronary artery occlusion. The importance of early T wave changes after thrombolytic therapy was evaluated by Richardson et al. (20) who reported a significantly faster reduction of T wave amplitude within 3 h after the initiation of thrombolytic therapy among patients with a patent infarct-related artery. However, they found no relation between these rapid repolarization changes and left ventricular function. To our knowledge, no other published study evaluated the significance of early T wave inversion after thrombolytic therapy.

The relatively small number of patients in this study calls for caution. However, the present study results do suggest a significantly more favorable in-hospital outcome in patients with early inversion of T waves. Thus, an early inversion of the T wave may indicate a physiologically successful reperfusion.

### References


