Significance of Initial ST Segment Elevation and Depression for the Management of Thrombolytic Therapy in Acute Myocardial Infarction

Jos L. Willems, MD, Rik J. Willems, BS, George M. Willems, PhD, Alfred E.R. Arnold, MD, Frans Van de Werf, MD, and Marc Verstraete, MD, for the European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator*

To determine the ability of initial ST segment elevation and depression to predict infarct size limitation by thrombolytic therapy, data were analyzed in 721 patients with acute myocardial infarction who were admitted to a randomized, placebo-controlled study of intravenous recombinant tissue-type plasminogen activator. Patients with QRS duration of 120 msec or more or with previous history of myocardial infarction were excluded, leaving 322 in the treatment and 333 in the placebo group. Cumulative 72-hour release of α-hydroxybutyrate dehydrogenase and global ejection fraction as well as left ventricular wall motion derived from angiography were used as independent measures of infarct size. Electrocardiograms obtained at admission, 6 hours after start of therapy, and before discharge were analyzed. All ST measurements were made by hand at the J point and 60 msec after the J point. Patients with high ST segment elevation at admission (i.e., sum of ST elevation at 60 msec after the J point was 20 mm or more) had significantly larger infarction and higher hospital mortality when compared with those with lower (<20 mm) ST elevation. Reciprocal ST segment depression also showed a linear relation with infarct size and mortality, independent from ST elevation, both in anterior and inferior myocardial infarction. The sum of deviations measured at the J point and 60 msec after the J point differed significantly, especially in anterior myocardial infarction at admission (mean, 16±9 versus 23±11 mm). The prognostic value of one measurement was not, however, superior over the other. Treatment with recombinant tissue-type plasminogen activator was most effective in those with large ST deviations at admission, but patients with anterior infarction and smaller ST shifts also appeared to benefit from therapy. Results in individual patients were variable, and the overall correlation of initial ST shifts with enzymatic infarct size was rather low. In conclusion, the present study shows that the magnitude of initial ST elevation and also of reciprocal ST depression in the admission electrocardiogram is valuable for the management and assessment of thrombolytic therapy in patients with acute myocardial infarction. (Circulation 1990;82:1147–1158)

Thrombolytic therapy of acute myocardial infarction (MI) is now an established component of coronary care. Several studies have demonstrated that early intravenous administration of thrombolytic agents in patients who present with ST segment elevation may reduce infarct size, limit left ventricular dysfunction, and lower both early and late mortality.1-2 The experimental foundation for the use of ST segment elevation as a reflection of myocardial injury was established in the early 1970s from epicardial and precordial electrocardiographic (ECG) mapping, both in experimental animals and in patients.3-6 As a result, ST segment elevations are routinely measured at admission to define subsets of patients that can benefit most from

* A listing of investigators and participating centers is given in the Appendix.

From the Divisions of Medical Informatics and Cardiology (J.L.W., R.J.W., F.V.d.W.), University of Leuven, Belgium; the Institute for Cardiovascular Research (G.M.W.), University of Limburg, The Netherlands; the Center of Clinical Decision Analysis and Thoraxcenter (A.E.R.A.), Erasmus University, Rotterdam, The Netherlands; and the Center for Thrombosis and Vascular Research (M.V.), University of Leuven, Belgium.

Address for reprints: Jos L. Willems, MD, Division of Medical Informatics, University Hospital Gasthuisberg, 49, Herestraat, 3000 Leuven, Belgium.

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early thrombolysis\textsuperscript{7-10} and even to monitor the effects of reperfusion therapy.\textsuperscript{11,12}

The significance and utility of ST segment depression as an independent measurement, however, is less than clear.\textsuperscript{1,13,14} In a recent review, Berger and Ryan\textsuperscript{14} reported that the majority of studies have shown that patients with inferior infarction associated with precordial ST segment depression have larger MIs than patients without precordial ST segment depression. Despite this finding, few studies have examined the impact of thrombolysis on this high-risk group.\textsuperscript{14} In anterior infarction, “reciprocal” ST depression has almost always been neglected.\textsuperscript{9} As a result, ST segment depression is not routinely used in the management and assessment of thrombolytic therapy.

In addition, little attention has been paid to the ST measurement methodology. Different authors have measured ST segment shifts at different time intervals (e.g., 0 msec,\textsuperscript{3,8,9,11} 20 msec,\textsuperscript{4,15,16} 40 msec,\textsuperscript{6,17,18} 60 msec,\textsuperscript{19} or 80 msec\textsuperscript{20-22} after QRS offset, 60 msec after the nadir of the S wave,\textsuperscript{5,23} or 140 msec after QRS onset,\textsuperscript{24} using either the TP or the PR segment as baseline. The ST segment is rarely horizontal; thus, differences in methodology result in different ST shifts, but quantitative data on these differences are yet unknown.

To resolve some of these issues, we analyzed data obtained in a double-blind, placebo-controlled, randomized trial of intravenous recombinant tissue-type plasminogen activator (rt-PA) in 721 patients with acute MI.

**Methods**

**Patients and Treatment Protocol**

The inclusion and exclusion criteria, as well as treatment protocol of the trial, have been published previously.\textsuperscript{25} A total of 721 patients were included from 26 participating centers, 366 in the placebo and 355 in the rt-PA treatment group. The present analysis was restricted to 655 cases with a first infarction and QRS duration of less than 120 msec. Patients aged 21–71 years with chest pain typical of myocardial ischemia for at least 30 minutes were eligible for the trial, provided therapy could be started within 5 hours after the onset of symptoms. ST segment elevation of at least 2 mm (measured 60 msec after the J point) had to be present in two or more limb leads or in leads V\textsubscript{5} and V\textsubscript{6}, or an elevation of 3 mm had to be present in two or more precordial leads. Patients with ST segment depression of 2 mm or more in two precordial leads, together with ST segment elevation of at least 1 mm in two limb leads or in leads V\textsubscript{5} and V\textsubscript{6}, indicating MI of the posterior wall, were also included. All patients received daily aspirin and heparin from the start of therapy until angiography was performed at 10–22 days after admission.

**Electrocardiographic Analysis**

ECGs obtained at admission, 6 hours after start of treatment, and before discharge were analyzed in the Core ECG Laboratory. Details of this analysis have been reported elsewhere.\textsuperscript{26} The ECG at discharge was recorded between 10 and 22 days after admission. Special forms were designed to record 98 primary measurements per ECG. These included all measurements needed to derive the full 54-criteria/32-point Selvester score\textsuperscript{27} as well as the Cardiac Infarction Injury Score.\textsuperscript{28} In addition, R wave and ST amplitude measurements were made in each lead, including lead aVR. ST was measured both at the J point and 60 msec after the J point. The reference baseline for all R and ST amplitude measurements was the PR segment immediately preceding QRS onset, as specified by Rautaharju et al.\textsuperscript{28} ST measurements are expressed in millimeters (1 mm=0.1 mV). ECGs were recorded in the standard manner on three-channel recorders at a paper speed of 25 mm/sec and at an amplification of 10 mm/mV. All measurements were made by hand, using a \times4 magnifying glass.

Results were stratified according to infarct location and the sum of ST elevation or ST depression at admission. Infarct location was determined on the basis of the admission ECG in the central ECG laboratory and was designated anterior in cases of ST elevation in leads V\textsubscript{1}–V\textsubscript{4} and inferior in cases of ST elevation in leads II, III, and aVF. In cases of ST elevation in leads I, aVL, V\textsubscript{5}, and V\textsubscript{6}, the location was designated anterior unless ST elevation was also present in leads II, III, or aVF or unless ST depression was present in leads V\textsubscript{1}–V\textsubscript{4}, in which case the location was determined as inferior. Cases with posterior or posterolateral MI were classified as inferior.\textsuperscript{9}

For anterior MI, the sum of ST elevation was calculated by adding all ST elevations present in leads I, aVL, and V\textsubscript{1}–V\textsubscript{4}.\textsuperscript{2} The same leads were used to calculate the sum of the R waves. The extent of epicardial injury was also quantified by counting the number of leads with ST elevation of 1 mm or more at point J.\textsuperscript{11} In case of inferior MI, the sum of R wave amplitudes was calculated in leads II, III, and aVF on the one hand and in leads II, III, aVF, I, aVL, V\textsubscript{5}, and V\textsubscript{6} on the other. For the sum of ST changes in inferior MI, ST elevations in leads II, III, aVF, I, aVL, V\textsubscript{5}, and V\textsubscript{6} and the absolute value of the ST depressions in leads V\textsubscript{1}–V\textsubscript{4} were added, in a manner similar to that in the study of Bår et al.\textsuperscript{9} The sum of ST elevation was also calculated separately for leads II, III, and aVF.\textsuperscript{11} Reciprocal ST changes, based on the sum of the ST segment depressions in leads II, III, and aVF for anterior MI and the sum of the ST depressions in leads V\textsubscript{1}–V\textsubscript{4} for inferior MI, were evaluated.

The cutoff points used for stratification according to ST segment deviations were defined before data analysis. They were based on the studies by Bår et al\textsuperscript{9}
and Aldrich et al,¹¹ who classified subgroups according to ST elevation. Rounded medians were used as cutoff points to stratify patients according to the size of reciprocal ST depression.

**Enzymatic Infarct Size and Left Ventriculography**

Infarct size was assessed in the Core Laboratory for Enzyme Determination by measurement of the cumulative release of α-hydroxybutyrate dehydrogenase (HBDH) during the first 72 hours, as reported elsewhere.²⁵ HBDH values were missing in 15 of the 655 cases analyzed in the present study. Global left ventricular ejection fraction and regional wall motion were derived from contrast left ventriculography, made 10–22 days after the onset of symptoms, in 530 patients. All films were examined centrally in the Core Laboratory for Quantitative Angiography.²⁵

**Statistical Analysis**

Frequency distributions were made first for all variables and subsequently for various subgroups, using the SAS statistical package. The hypothesis that no differences were present in different groups was tested by using χ² (with Yates' correction) Fisher's exact tests for categorical variables and Student's t tests for continuous variables, if the frequency distribution of the data permitted such analysis. The Wilcoxon-Mann-Whitney test was used to compute the significance of differences in median values of cumulative HBDH release. Mean±1 SD is given for the other variables. The association between the sum of ST deviations at admission and enzymatic, angiographic, or other ECG estimates of infarct size was evaluated by simple and multiple linear regression analysis. The same technique was used to evaluate the prediction formulas developed by Aldrich et al.¹¹

**Results**

**Size and Regression of ST Changes**

The size of ST deviations measured at admission, 6 hours after start of therapy, and in the predischarge ECG are listed in Table 1, both for the sum of the ST deviations measured at the J point and 60 msec after the J point. ST deviations measured 60 msec after J were significantly greater than those at the J point, especially in anterior MI (p<0.001). In inferior MI, these differences were less pronounced but still significant at admission (see Figure 1).

The extent of initial epicardial injury, as assessed by the number of leads with ST elevation of 1 mm or more at admission, was the same in both treatment groups. The average number of leads with ST elevation was 5.0±1.8 in the rt-PA–treated patients and 5.0±1.6 in the placebo-treated patients with anterior MI.

ST deviations regressed significantly faster in the rt-PA group than in the placebo group (Table 1). The sum of ST measured 60 msec after the J point fell by 13.8±9.8 mm in the rt-PA group compared with 9.6±11.0 mm in the placebo group between admission and 6 hours later; a further decrease of 1.6±5.6 mm in the rt-PA group compared with 5.2±8.4 mm in the placebo group was measured before discharge.

**Table 1. Regression of the Sum of ST Deviations in Patients Treated With Recombinant Tissue-Type Plasminogen Activator and With Placebo**

<table>
<thead>
<tr>
<th>ECG</th>
<th>At admission</th>
<th>After 6 hours</th>
<th>After 10–22 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rt-PA</td>
<td>Placebo</td>
<td>rt-PA</td>
</tr>
<tr>
<td>Total group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>322</td>
<td>333</td>
<td>313</td>
</tr>
<tr>
<td>Σ-ST-60 (mm)</td>
<td>20.1±10.7</td>
<td>19.9±12.0</td>
<td>6.3±6.2</td>
</tr>
<tr>
<td>Σ-ST-J (mm)</td>
<td>15.8±8.4†</td>
<td>15.8±10.2†</td>
<td>5.3±5.4†</td>
</tr>
<tr>
<td>Anterior MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>126</td>
<td>109</td>
<td>117</td>
</tr>
<tr>
<td>Σ-ST-60 (mm)</td>
<td>22.8±11.0</td>
<td>24.9±13.0</td>
<td>10.0±5.9</td>
</tr>
<tr>
<td>Σ-ST-J (mm)</td>
<td>16.1±8.5†</td>
<td>17.9±13.1†</td>
<td>7.2±4.9†</td>
</tr>
<tr>
<td>Inferior MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>195</td>
<td>222</td>
<td>195</td>
</tr>
<tr>
<td>Σ-ST-60 (mm)</td>
<td>18.4±10.1</td>
<td>17.7±10.6</td>
<td>4.2±5.3</td>
</tr>
<tr>
<td>Σ-ST-J (mm)</td>
<td>15.7±8.3†</td>
<td>15.0±8.2†</td>
<td>4.2±5.4</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.

ST deviations are measured at the J point (Σ-ST-J) and 60 msec after the J point (Σ-ST-60). For anterior MI (myocardial infarction), values represent sum of ST elevation in leads I, aVL, and V₅₋₆. For inferior MI, values represent ST elevations in leads II, III, aVF, I, aVL, V₅, and V₆ plus ST depression in leads V₅₋₆.

*p<0.0001 compared with corresponding value for recombinant tissue-type plasminogen activator (rt-PA) treatment.

†p<0.0001 compared with Σ-ST-60 group.

‡p<0.01 compared with rt-PA treatment.

§p<0.01 compared with Σ-ST-60 group.

[p<0.001 compared with rt-PA treatment. ]
The sum of ST measured at the J point decreased 10.5±8.5 mm in the rt-PA group compared with 7.0±10.4 mm in the placebo group in the first 6 hours; further decrease of 1.8±5.3 mm and 5.1±7.9 mm, respectively, was measured before discharge.

Irrespective of treatment and infarct location, patients with ≥60% reduction in SUM-ST within the first 6 hours (n=344) had 21% smaller mean Selvester score results at discharge (5.57±4.11 vs. 7.06±3.88, p<0.001) and 24% less HBDH release (median, 685 vs. 901 u/I; p<0.001) than those (n=272) with <60% early ST normalization.

**ST Changes at Admission and Estimates of Infarct Size**

Patients with large ST deviations at admission had larger enzymatic and ECG estimates of infarct size, more reduced left ventricular function, and a higher hospital mortality (see Table 2) than those without large ST deviations. For all measurements, the results indicated an infarct size reduction in the rt-PA group compared with the placebo group. Differences in HBDH release and ejection fraction between the rt-PA and placebo groups were more pronounced in patients with large ST deviations (see Table 2 and Figure 2). The difference in HBDH release between rt-PA and placebo groups was 3.5% (p=NS) when the sum of ST segment elevation measured 60 msec after the J point at admission was 12 mm or less, 15.5% (p<0.05) when this sum was more than 12 and less than 20 mm, and 22.7% (p=0.003) when this sum was 20 mm or more. The absolute difference in mean ejection fraction between the rt-PA and placebo groups amounted to 1.0%, 2.0% (both p=NS), and 3.5% (p<0.05) in these subgroups, respectively.

Similar results were obtained when the results were stratified according to ST deviations measured at the J point.

**Figure 1.** Bar graphs showing mean ST elevation (Σ-ST↑) and "reciprocal" ST depression (Σ-ST↓) in the admission electrocardiograms of the total patient population. Results have been stratified according to successive 5-mm levels of ST elevation measured at the J point (Σ-ST-J) and at 60 msec after the J point (Σ-ST-60). The scale of the ST depression has been magnified three times. Note that the difference between Σ-ST-60 and Σ-ST-J increases progressively. In inferior infarction, a progressive increase in the sum of ST elevation is accompanied with progressive, larger reciprocal ST depression. In anterior infarction, such a relation is not apparent. N, number of patients.

**Figure 2.** Bar graphs showing mortality within 10–22 days after onset of symptoms (upper panel) and α-hydroxybutyrate dehydrogenase (HBDH) release (lower panel) according to different levels of ST deviations measured 60 msec after the J point (SUM-ST-60) (see Table 1) at admission, in the recombinant tissue-type plasminogen activator (rt-PA) and placebo groups.
Table 2. Estimates of Infarct Size According to the Sum of ST Elevation at Admission

<table>
<thead>
<tr>
<th></th>
<th>Σ-ST-60</th>
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<tbody>
<tr>
<td></td>
<td>≤12 mm</td>
</tr>
<tr>
<td>Admission ECG</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>rt-PA</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Predischarged ECG</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>80</td>
</tr>
<tr>
<td>Selvester score</td>
<td>4.84±3.75</td>
</tr>
<tr>
<td>CIIS</td>
<td>25.1±10.9</td>
</tr>
<tr>
<td>No. of Q waves</td>
<td>1.48±1.31</td>
</tr>
<tr>
<td>HBDH release</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>82</td>
</tr>
<tr>
<td>Median (units/l)</td>
<td>581</td>
</tr>
<tr>
<td>Q1–Q3 (units/l)</td>
<td>325–801</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>69</td>
</tr>
<tr>
<td>%</td>
<td>54.0±9.4</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.

Σ-ST-60, ST deviation measured at 60 msec after the J point; rt-PA, recombinant tissue-type plasminogen activator; ECG, electrocardiogram; n, number of patients; CIIS, Cardiac Infarction Injury Score; HBDH, α-hydroxybutyrate dehydrogenase.

For HBDH release, medians and 25–75% quartile intervals (Q1–Q3) are given.

*p=0.08 compared with mortality in the corresponding rt-PA group.

†p<0.01 compared with rt-PA group.

‡p<0.05 compared with rt-PA group.

§p=0.07 compared with corresponding result in the rt-PA group.

Table 3. Inferior Infarction: Estimates of Infarct Size According to ST Depression Measured 60 msec After the J Point in Leads V1–V4 in the Admission Electrocardiogram

<table>
<thead>
<tr>
<th></th>
<th>Σ-ST-60 depression in leads V1–V4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥−5.5 mm</td>
</tr>
<tr>
<td>Admission ECG</td>
<td>rt-PA Placebo</td>
</tr>
<tr>
<td>n</td>
<td>91 119</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>1.1</td>
</tr>
<tr>
<td>Predischarged ECG</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>89 111</td>
</tr>
<tr>
<td>Selvester score</td>
<td>4.87±3.92</td>
</tr>
<tr>
<td>CIIS</td>
<td>25.4±10.0</td>
</tr>
<tr>
<td>HBDH release</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>90 118</td>
</tr>
<tr>
<td>Median (units/l)</td>
<td>578 715‡</td>
</tr>
<tr>
<td>Q1–Q3 (units/l)</td>
<td>330–801 430–987</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>76 100</td>
</tr>
<tr>
<td>%</td>
<td>55.1±8.8</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.

Σ-ST-60, ST deviation measured at 60 msec after the J point; rt-PA, recombinant tissue-type plasminogen activator; ECG, electrocardiogram; n, number of patients; C.I.I.S., Cardiac Infarction Injury Score; HBDH, α-hydroxybutyrate dehydrogenase.

For HBDH release, medians and 25–75% quartile intervals (Q1–Q3) are given.

*p=0.08 compared with mortality in the corresponding rt-PA group.

†p<0.01, ‡p<0.05, and §p<0.001 compared with rt-PA group.
Univariate Results According to Reciprocal ST Changes

Patients with inferior MI and large ST depressions in leads V₁–V₄ in the admission ECG, that is, greater than 5.5 mm (the median value, measured 60 msec after the J point), developed larger infarcts and had a significantly higher hospital mortality (see Table 3). In patients with large reciprocal ST changes, HBDH release was 23% \((p<0.01)\) lower, and left ventricular ejection fraction was 3.6% \((p<0.05)\) better in the rt-PA group compared with the control group. However, differences in the QRS score results in the predischARGE ECG did not reach the \(p<0.05\) significance level. Akinnesia or dyskinesia of the anterolateral or anteroseptal left ventricular wall was no more frequent in patients with large (15 of 196 patients) as opposed to small (14 of 201 patients) ST depression in leads V₁–V₄.

Patients with anterior MI and large reciprocal ST depressions in leads II, III, and aVF in the admission ECG also developed larger infarcts and showed a higher hospital mortality (see Table 4). The mortality of the rt-PA patients was half that of the placebo cases; due to the small numbers involved, this difference was not statistically significant. All QRS estimates of infarct size measured at discharge were also lower in the rt-PA than the placebo group. Those with extensive ST depression in the inferior leads (sum of ST deviation in leads II, III, and aVF \(\geq 2.0\) mm) had only slightly more akinzenia or dyskinesia of the diaphragmatic wall (25.2%; 29 of 115 patients) than those with less ST depression (21.4%; 21 of 98 patients from the rt-PA and placebo group combined). This percentage was greater (33.3%) in those with ST elevation in the inferior leads (sum of ST deviation in leads II, III, and aVF \(\geq 2.0\) mm). The median HBDH release in this group (625 units/l; Q₁–Q₃ quartiles, 394–811 units/l; \(n=18\)) was lower \((p=0.07)\) than in those with sum of ST deviation in leads II, III, and aVF of \(\geq 2.0\) mm or more and less than 2.0 mm (799 units/l; Q₁–Q₃ quartiles 493–1,235; \(n=99\)). These cases (rt-PA and placebo group combined) also showed significantly \((p<0.01)\) fewer Q waves in the predischARGE ECG \((1.13\pm 1.67)\) as opposed to 2.76±2.11 in those with intermediate and 2.69±1.77 in those with large ST depression in the inferior leads).

Simple Regression Analysis Results

Simple regression analysis between the sum of ST deviation measured at admission and HBDH release resulted in a correlation coefficient of 0.32 both for ST deviation measured at the J point and for ST deviation measured 60 msec after the J point in the total patient population \((n=635)\). Corresponding figures for angiographic-determined ejection fraction \((n=529)\) were \(r=0.25\) and \(r=0.24\), respectively. Correlation coefficients were slightly higher in the placebo patients \((r=0.38\) in anterior MI and 0.35 in inferior MI) than in the rt-PA patients \((r=0.26\) and 0.22, respectively). The correlation between ST deviation at admission and the Selvester or cardiac infarction injury score measured at discharge was also very low (between 0.15 and 0.26 for the patients
TABLE 5. Multiple Regression Analysis of $\alpha$-Hydroxybutyrate Dehydrogenase Release Versus Initial ST Elevation and Reciprocal ST Depression

<table>
<thead>
<tr>
<th>Subgroup*</th>
<th>n</th>
<th>Multiple regression equation</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior MI (n=218)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J+60 SD</td>
<td>Y = 444 + 16.5 X1 - 70.8 X2</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>(103) (3.9) (15.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J+60 p</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior MI (n=411)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J+60 SD</td>
<td>Y = 570 + 15.7 X1 - 11.0 X2</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>(48) (4.2) (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J+60 p</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>&lt; 0.0002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| MI, myocardial infarction; n, number of patients; J+60, ST measurement at 60 msec after the J point; Y, $\alpha$-hydroxybutyrate dehydrogenase release; X1, initial ST elevation; X2, reciprocal ST depression; J, ST measurement at the J point; R, multiple correlation coefficient.

*rt-PA and placebo group combined.

included in the study, excluding cases with QRS ≥ 120 msec or previous MI). Predicted infarct size according to the formulas developed by Aldrich et al.11 had a rather low correlation with the Selvester score results obtained from the discharge ECG (maximum r = 0.30), HBDH release (maximum r = 0.35), and ejection fraction (maximum r = -0.45) in the total patient population and both treatment groups separately.

Independent Contribution of ST Depression From ST Elevation

Multiple regression analysis (see Table 5) demonstrated a significant and independent correlation of initial ST elevation and reciprocal ST depression with HBDH release. Multiple correlation coefficients were significantly higher in anterior than inferior infarction. Addition of the treatment code as the third independent variable did not distort this relation. Correlation coefficients obtained from the placebo group were significantly higher than those obtained from the rt-PA group (see Table 5).

The independent contribution of ST depression and ST elevation in predicting infarct size, as estimated by HBDH release and short-term mortality, is further illustrated in Figure 3. In patients with similar degrees of ST segment elevation, reciprocal ST segment depression exceeding median values is associated with 15–24% greater infarct size, both in inferior and anterior infarction, when compared with patients with lower ST depression. Anterior infarction patients with a sum of ST elevation of less than 20 mm in the anterior leads (V1–V6, I, and aVL) and a sum of ST depression of -2 mm or more in the inferior leads (II, III, and aVF) had a short-term mortality of 0%, in both the rt-PA and the placebo groups. However, rt-PA patients still had 10% lower HBDH release compared with the placebo group (median, 660 versus 734 units/l, respectively). On the contrary, patients with inferior infarction, treated

FIGURE 3. Bar graphs showing relation of $\alpha$-hydroxybutyrate dehydrogenase (HBDH) release and short-term mortality (in percent) with different levels of ST elevation in the admission electrocardiogram and the presence of "reciprocal" ST depression in patients with anterior and inferior infarction. Rounded medians were used as cutoff values for the stratification of ST elevation (Σ-ST-60 †) and ST depression (Σ-ST-60 ‡). rt-PA, treatment with recombinant tissue-type plasminogen activator.
with rt-PA as compared with placebo, had neither a reduction in short-term mortality (1.6% versus 1.3%, respectively) nor a reduction in HBDH release (median, 578 versus 591 units/l, respectively) when only small ST elevations in the inferior leads and small reciprocal ST depressions in leads V₁–V₄ were present in the admission ECG. The independent contribution of ST segment depression from ST elevation was also apparent in the ejection fraction results. Indeed, rt-PA and placebo patients with anterior infarction and large ST elevation (≥20 mm) in the anterior leads had an ejection fraction of 40.3±8.4% and 41.8±13.6%, respectively, when the sum of reciprocal ST depression was less than −2 mm, against 51.4±10.7% and 45.1±12.9%, respectively, when reciprocal ST depression was −2 mm or more.

**Discussion**

In the trial that forms the basis for the present analysis, intravenous rt-PA reduced enzymatic infarct size, as determined by HBDH release, by 20% (p<0.002), preserved left ventricular function, and lowered early mortality of acute MI by 51% (confidence interval, −76 to 1).²⁵

**Importance of Large ST Deviations at Admission**

The present study corroborates findings of other investigators,⁸,⁹ who demonstrated that early thrombolytic therapy results in the largest limitation of enzymatic infarct size in patients with extensive myocardial ischemia, as reflected by high ST segment deviations. We found a higher mortality and larger infarct size in patients with large ST deviations (sum of ST deviation at 60 msec after the J point ≥20 mm) at admission than in those with small ST deviation (<12 mm). The effect of rt-PA was significantly more pronounced in those with large than in those with small ST deviation. This was true in anterior as well as inferior infarction.

Whereas the value of ST elevation as an indicator of myocardial injury has been firmly established for many years,³–⁶ controversy still prevails on the value of reciprocal ST depression. Some investigators found no correlation of enzymatic or angiographic infarct size with precordial ST segment depression in evolving inferior MI²⁵ or ST depression in the inferior leads in evolving anterior MI; others found positive correlations.¹³,¹⁴,²⁰,²⁴ In all these studies, only univariate analysis was performed. In the present study, multivariate analysis was performed. Results demonstrate that the presence versus the absence of reciprocal ST segment depression, independently of ST elevation, does add clinically important information with regard to predicting larger enzymatic infarct size and predicting higher short-term mortality, both in inferior and anterior infarction.

**Significance of Reciprocal ST Changes in Inferior MI**

Findings of the current study support the views expressed in a recent editorial by Boden and Spodick,¹³ who reported that ST segment depression in leads V₁–V₄ associated with evolving inferior infarction reflects, in the majority of cases, inferior-posterior wall injury and not remote anterior wall ischemia; others¹⁴ have reported that remote ischemia can definitely be present in some cases with multiple vessel disease.¹³ This is corroborated by recent findings of Sato et al.,³⁰ who measured precordial ST shifts and myocardial lactate metabolism during coronary angioplasty of the right coronary artery. Patients with large ST depression in V₁–V₄, similar to those with less or no ST depression, had an increase in lactate extraction from the area supplied by the left anterior descending artery and not an excess lactate production, as one would expect in the case of anterior wall ischemia. Akinesia or dyskinesia of the anteroseptal and anterolateral left ventricular region was no more common in cases with large ST depression in V₁–V₄ than in those with smaller ST depression in the present study. In patients with true posterior infarction, reciprocal ST depression in these leads, even as the only manifestation of injury, should not preclude the installment of thrombolytic therapy.¹³ Mortality and HBDH data from the present study demonstrate that large ST segment depressions at admission in leads V₁–V₄ in patients with evolving inferior MI are indicative of a potentially large infarct. As a result, such cases may benefit more from thrombolysis than those with smaller reciprocal ST shifts. Indeed, hospital mortality was reduced from 6.8% to 1.9% by rt-PA in those patients in which the sum of ST depression in leads V₁–V₄ was greater than 5.5 mm; mortality was reduced from 1.7% to 1.1% in those patients in which this sum was 5.5 mm or less.

**Significance of Reciprocal ST Changes in Anterior MI**

Large reciprocal ST shifts at admission are indicative of a large jeopardized zone of myocardium also found in anterior MI. Patients with evolving anterior MI and large ST depression in the inferior leads (i.e., sum of ST deviations in leads II, III, and aVF < −2.0 mm) had a mortality that was more than twice that of patients in which this sum was −2.0 mm or more. Treatment with rt-PA reduced mortality in these groups from 14.3% to 7.9% and from 6.7% to 3.2%, respectively.

Lew et al.²⁰ have suggested that inferior ST changes in acute anterior MI may be confounded by concomitant ischemia of the inferior wall, as a result of the occlusion of a long left anterior descending artery that may go around the apex and supply the diaphragmatic wall. We found diaphragmatic wall motion abnormalities in about 25% of patients with anterior MI, but neither the magnitude nor the sign of the inferior ST shifts predicted their occurrence. These findings suggest that, in a number of cases with acute anterior MI, inferior ST depression is also due to a reciprocal effect and not to ischemic involvement of an additional area of the left ventricle. However, the standard ECG is not well suited to reflect the
reciprocal of anterior injury current, since leads on the back are not recorded routinely. Only leads I and aVL are more or less opposite to leads II, III, and aVF. This explains why the amount of ST depression in the inferior leads did not correlate well with the level of ST elevation in the anterior leads in the current study.

As in the study of Lew et al.,20 patients with anterior MI and inferior ST elevation tended to have smaller HBDH enzyme release and fewer Q waves at discharge, the reasons of which remain obscure. The observation that reciprocal ST depression is correlated with measures of infarct size, independent from ST elevation, suggests that remote ischemia may be present in the region contralateral from the infarcted zone, at least in some cases. Such ischemia has been demonstrated in a few cases by positron emission tomography31 and has also been suggested recently by body surface mapping.32

**Standardization of ST Measurement Methodology**

Different methodologies for measurement of ST have been applied by various authors, which make comparison of quantitative data difficult. The time at which ST is measured, in particular, differed widely in different studies. Controversy also exists regarding the use of the TP or PR segment as baseline.

As advocated by Rautaharju et al.28 and other investigators33 focusing on quantitative electrocardiography, we have systematically used the PR segment as baseline for all QRS and ST measurements. From a pragmatic point of view, this is easier and more consistent than using the TP segment if the heart rate is slow and the PR segment when the heart rate is fast and no TP segment can be seen. A measurement procedure that may change suddenly with a small change in heart rate is certainly not optimal. In addition, the presence of a U wave often complicates the determination of the end of the T wave and the TP segment. The reproducibility for determining accurately the onset of QRS is far greater than that for determining the end of the T wave.34 As a result, for computer analysis of the resting ECG as well as the exercise ECG and body surface mapping, a horizontal level defined within an interval immediately preceding QRS onset is generally used for all QRS and ST-T amplitude measurements.

With respect to the time location at which ST measurements are to be made, either the J point or the J point plus 60 msec can be used. The present study shows that, especially in anterior MI, large differences can be seen between ST measurements made at these two points. However, correlation data with respectively enzymatic and angiographic estimates of infarct size were not significantly different for sum-ST measured at the J point or 60 msec later. Therefore, either of these two methods may be used, but standardization should be recommended for quantitative measurement of ST elevation and depression. In some studies, ST elevation was measured 20 msec after the J point and ST depression at the J point plus 80 msec.15,29 Such a measurement strategy should, in our opinion, not be recommended. Indeed, ST injury measurements change with time and so could the time location of ST measurement. In addition, considerable variability would occur when the ST segment is in the vicinity of the baseline. We recommend that ST measurements be made at one fixed time point, whether there is ST elevation or depression.

**Clinical Implications**

The present study demonstrates that not only ST elevation but also reciprocal ST depression are useful for predicting the evolving infarct size at admission and for guiding management of thrombotic therapy. Our findings demonstrate that the sum of initial ST elevation and of the contralateral ST depression reflect the extent of ischemic injury, in inferior and also anterior MI. The total amount of ST shifts measured at admission bear a linear relation to total HBDH release and reflect hospital mortality and predischarge left ventricular ejection. Results of the present study indicate that a summed amount of ST deviation less than 12 mm, measured in the admission ECG 60 msec after the J point, predicts a low probability of benefit from thrombotic therapy. Nevertheless, some indexes reflecting infarct size limitation still favored rt-PA over placebo, also for these cases. However, patients with inferior infarction and both low ST elevation (<10 mm) and low reciprocal ST depression (<5.5 mm) showed almost no benefit from thrombolysis.

It must be taken into consideration that ejection fraction was measured at catheterization, 10–22 days after infarction. In some cases, especially in the placebo group, catheterization could not be performed since the patient died before the procedure. It is reasonable to assume that cases with extensive damage were saved by rt-PA therapy, causing selection bias at the end. This may have affected the results. In all probability, the difference in ejection fraction, as well as enzyme release, between the rt-PA and placebo groups, would have been more striking if results had been available for all cases.26,35

In addition to ischemia, the ST segment is influenced by many factors. Since intraventricular conduction disturbances are almost always associated with secondary ST-T changes when QRS duration is greater than 120 msec, we have excluded these patients from the study. Patients with previous infarction were also excluded, since they may have residual ST deviations independent from the new event. Other factors, such as marked variations in electrolytes, the development of pericarditis or pericardial effusion, acute right ventricular overload, and the use of digitalis and other drugs can also alter ST segment measurements independent of changes in ischemic injury.4–6 In addition, although a magnifying glass was used, manual measurements suffer from well-known interobserver and intraobserver variabil-
The effects of these uncontrolled variables as they apply to the monitoring of thrombolytic therapy, as well as differences in time of recording (between 0 and <5 hours after onset of symptoms), were countered in the present study by comparing patients randomly assigned to rt-PA and placebo treatment. In a previous publication on the European rt-PA placebo trial,25 it was demonstrated that randomization achieved good results. Baseline characteristics on admission were not significantly different in the two patient groups. Serum potassium level at admission was 3.95±0.62 meq/l and 4.02±0.64 meq/l in the placebo-treated and rt-PA-treated patients, respectively. Fifty patients in the placebo group and 44 in the rt-PA group had a potassium level of less than 3.5 meq/l; 1.8% and 0.6%, respectively, received digitalis at admission.

In accordance with several other investigations,3,5,7,9,15–17,24,36 the present study shows that the standard ECG has definite ability to recognize and predict differing patterns of infarct evolution in patient groups of sufficient sample size. However, in the individual patient, the prognostic merits of the 12-lead ECG are more limited.10 Despite the intrinsic limitations of the surface ECG, we believe that computer technology can enhance the use of this cheap and noninvasive tool by providing standardized QRS and ST-T measurements33,34 and by providing new ways of quantitative analysis and display.12,37 From a pragmatic point of view, such enhancement is probably more acceptable for clinicians in routine practice than the promotion of body surface mapping, although this technique may be more sensitive than standard ECG at least in anterior MI cases.23,24

Finally, the results of the present study underscore the potential benefit of intravenous rt-PA therapy in patients with evolving infarction and emphasize that the extent of this benefit will vary with the amount of myocardium at risk. This can be assessed by the magnitude of ST shifts on the admission ECG. Although mortality and several measures of infarct size were consistently reduced by rt-PA therapy, statistical significance levels were not reached in several subgroups, because of limitations of sample size.

It was interesting to note that patients with the fastest reduction of ischemic ST changes (i.e., ≥60% reduction of SUM-ST in the first 6 hours, had on the average 20–25% smaller infarcts, as estimated from the Selvester score at discharge and by cardiac enzymes, than those with <60% ST normalization in that time, irrespective of treatment and infarct location. These results corroborate clinical observations that indicate that fast reduction and disappearance of ischemic pain and ST changes are a reflection of early recanalization and can be used for noninvasive monitoring of perfusion.

Appendix: European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator Participating Clinics

Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium (H. De Geest, F. Van de Werf, A. Beernaert); H. Hartkliniek, Neerpelt, Belgium (A. van Dorpe); O.C.M.W. St. Elisabeth, Turnhout, Belgium (H. Lesselier, D. Engelaar); St. Jozefkliniek, Ostend, Belgium (R. Stroobandt, G. Holvoet); H. Hartziekenhuis, Roeselare, Belgium (B. Beverwaert, D. Clement); St. Elisabethziekenhuis, Geel, Belgium (J. Schuermans, M. Vermeire); Imelda Ziekenhuis, Bonheiden, Belgium, (L. Hermans, G. Verstreken); St. Jozefziekenhuis, St. Truiden, Belgium (J. Beckers, H. Robijns); St. Elisabethziekenhuis, Herentals, Belgium (S. De Schepper); H. Hartziekenhuis, Tienen, Belgium (L. De Wolf, H. Van der Linden); St. Norbertusziekenhuis, Duffel, Belgium (U. Van Walleghem); Virga Jesse Ziekenhuis, Hasselt, Belgium (R. Geuken, J. Maris); Onze Lieve Vrouw Kliniek, Tongeren, Belgium (F. Gielen); Leyenburg Ziekenhuis, The Hague, The Netherlands (G.A. van der Kley); van Dam-Bethesda Ziekenhuis, Rotterdam, The Netherlands (J.W. Deckers); Kantonsspital, Basel, Switzerland (M. Pfisterer, F. Burkart); Centre de Reanimacions Cardiaca Unitat Coronar, Manresa, Spain (L.L. Jodar, P.X. Boada, P.S., E.J. Corsorns); Hospital Mutua de Terrassa, Barcelona, Spain (L. Saenz, S. Quintana, A. Alvarez, J.M. Nava, M. Alvarez); Royal Infirmary, Edinburgh, Scotland (D. De Bono, D. Ettles); Freeman Hospital, Newcastle-upon-Tyne, England (D.S. Reid, M. Beem); Stobhill General Hospital, Glasgow, Scotland (W.S. Hills, K.J. Hogg, R.S. Hornung, J.M.A. Burno, F.G. Dunn, A.P. Rae, M. Sandler); Medisch Centrum, Alkmaar, Alkmaar, The Netherlands (C. Burgersdijk, J. Ruiter); St. Franciscus Ziekenhuis, Roosendaal, The Netherlands (R.J. Bos); Akademika Sjukhuset, Uppsala, Sweden (B. Lagerqvist); Hospital de la Princesa, Madrid, Spain (C. Romero, X. Ruiz-Ocana, A. Reyes); Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (J. Garcia-Moll, X. Garcia-Picart).

Steering Committee


Data Monitoring and Ethical Committee

J. Hampton (Nottingham, England), D.G. Julian (Newcastle-upon-Tyne, England), W. Schaper (Bad Nauheim, FRG), L. Wilhelmsen (Göteborg, Sweden), D. Wood (Southampton, England).

Angiography Assessment Group

ECG Assessment Group
J.L. Willems (Leuven, Belgium), R. Doerr (Aachen, FRG).

Exercise Test Assessment Group
R. von Essen (Munich, FRG), J.M. Detry (Brussels, Belgium).

Radionuclide Assessment Group
J. Vanhaecke (Leuven, Belgium), L. Mortelmans (Leuven), J. Melin (Brussels, Belgium).

Central Coagulation Laboratory

Core Laboratory for Enzyme Determination

Core Laboratory for Quantitative Angiography

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