Change in ST segment elevation 60 minutes after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes

I F Purcell, N Newall, M Farrer

Abstract

Objective—To compare prospectively the prognostic accuracy of a 50% decrease in ST segment elevation on standard 12-lead electrocardiograms (ECGs) recorded at 60, 90, and 180 minutes after thrombolysis initiation in acute myocardial infarction. Design—Consecutive sample prospective cohort study. Setting—A single coronary care unit in the north of England. Patients—190 consecutive patients receiving thrombolysis for first acute myocardial infarction. Interventions—Thrombolysis at baseline. Main outcome measures—Cardiac mortality and left ventricular size and function assessed 36 days later.

Results—Failure of ST segment elevation to resolve by 50% in the single lead of maximum ST elevation or the sum ST elevation of all infarct related ECG leads at each of the times studied was associated with a significantly higher mortality, larger left ventricular volume, and lower ejection fraction. There was some variation according to infarct site with only the 60 minute ECG predicting mortality after inferior myocardial infarction and only in anterior myocardial infarction was persistent ST elevation associated with worse left ventricular function. The analysis of the lead of maximum ST elevation at 60 minutes from thrombolysis performed as well as later ECGs in receiver operating characteristic curves for predicting clinical outcome. Conclusion—The standard 12-lead ECG at 60 minutes predicts clinical outcome as accurately as later ECGs after thrombolysis for first acute myocardial infarction. (Heart 1997;78:465–471)

Keywords: myocardial infarction; thrombolysis; ST segment elevation

The aim of thrombolysis in acute myocardial infarction (AMI) is early and complete myocardial reperfusion. Incomplete or delayed reperfusion is associated with an increased risk of death and left ventricular dysfunction. TIMI grade 3 flow in the infarct related coronary artery is only achieved in 54% of patients by 90 minutes with front loaded tPA and in 31% of patients receiving streptokinase. While the choice of thrombolytic may change the outcome many patients have suboptimal reperfusion after standard thrombolytic regimens. While there is no proved advantage in routine post-thrombolytic coronary angiography after thrombolysis, rescue therapy may benefit a proportion of patients with suboptimal reperfusion provided they can be identified sufficiently early for myocardial salvage to take place. Immediate post-thrombolytic coronary angiography to identify high risk patients is not a practical option for most district general hospitals, nor is it desirable for all patients. Therefore a practical non-invasive marker of reperfusion is required to identify those patients who might benefit from rescue strategies.

The post-thrombolytic electrocardiogram (ECG) has shown promise as a non-invasive marker of reperfusion. Previous studies have shown an association between early resolution of ST elevation after thrombolysis and improved coronary patency and clinical outcome but its practical value as a prognostic marker remains controversial. Data are lacking regarding the predictive value of ECGs recorded within 90 minutes of thrombolysis, which is the period when early prognosis is largely determined. Continuous ST segment monitoring is useful in predicting coronary artery patency 60 to 90 minutes after initiation of thrombolysis but its application in clinical practice is restricted by its technical complexity (up to 40% of recordings may be unsatisfactory) and it is of unconfirmed value predicting clinical outcome. Early angiographic studies of thrombolysis suggested that most successful reperfusions occur within 60 minutes of thrombolysis, which, in combination with data from continuous ST monitoring, strongly suggests that the 12-lead ECG at 60 minutes could be used to predict clinical outcome. We therefore compared the accuracy of the 60 minute ECG with 90 minute and 180 minute ECGs for predicting 30–36 day clinical outcome.

Methods

PATIENTS

Eligible patients received thrombolysis within 12 hours of a first AMI. All had chest pain for 30 minutes or greater and ST elevation in two or more leads on a standard 12-lead ECG (0.1 mV limb leads, 0.2 mV chest leads). There was no age limit and the conventional contraindications to thrombolysis were observed. Streptokinase (1.5 MU intravenously over 60 minutes) was...
Baseline characteristics

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anterior MI</th>
<th>Inferior MI</th>
<th>All patients (anterior, inferior, and lateral MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>99 (53)</td>
<td>88 (47)</td>
<td>190 (100)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>65.3 (10.4)</td>
<td>62.0 (10.7)*</td>
<td>63.8 (10.7)</td>
</tr>
<tr>
<td>Age &gt; 75 (%)</td>
<td>15 (15)</td>
<td>7 (8)</td>
<td>24 (13)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>7 (7)</td>
<td>7 (8)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>29 (30)</td>
<td>16 (18)</td>
<td>45 (24)</td>
</tr>
<tr>
<td>Smoking</td>
<td>40 (40)</td>
<td>46 (52)</td>
<td>88 (46)</td>
</tr>
<tr>
<td>Current (%)</td>
<td>22 (22)</td>
<td>14 (15)</td>
<td>35 (18)</td>
</tr>
<tr>
<td>Never (%)</td>
<td>36 (36)</td>
<td>25 (28)</td>
<td>62 (33)</td>
</tr>
<tr>
<td>Pain to needle time (min)†</td>
<td>160 (70–600)</td>
<td>180 (60–435)</td>
<td>180 (70–456)</td>
</tr>
<tr>
<td>Door to needle time (min)†</td>
<td>30 (15–150)</td>
<td>30 (10–65)</td>
<td>30 (10–115)</td>
</tr>
<tr>
<td>tPA used (%)</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

*p < 0.05; †median time (10th–90th percentile).

Infarction. ECGs were performed by two experienced operators (IFP, MF) using a Hewlett-Packard Sonos 1500 echocardiography machine. Two mutually perpendicular long-axis planes through the left ventricle were obtained from a single apical position. The end-systolic and end-diastolic endocardial borders were traced and measured. The volumes were calculated using a method of disks algorithm and averaged for the three views over three consecutive cardiac cycles. LV volume indices were derived using estimated body surface areas. The LV ejection fraction (LVEF) was calculated from these volumes. An LVEF of < 0.4 was chosen to indicate poor LV systolic function.

Results

Baseline characteristics

Of the 332 consecutive patients with AMI, 262 (79%) underwent thrombolysis. Forty-seven had previous AMI and were not enrolled in this trial. Two hundred and fifteen patients were screened and 20 were excluded: 14 because the baseline ECG or all subsequent ECGs had uninterpretable ST segments because of conduction abnormalities. Five patients were excluded because of non-cardiac death (one cerebral infarction, two cerebral haemorrhage, one peripheral embolism, one pulmonary tuberculosis), one because of death of unknown cause. Five otherwise suitable patients did not have appropriately timed ECGs recorded and could not be enrolled, including one who died before the 60 minute ECG. One hundred and ninety patients who received thrombolysis for first AMI were therefore studied. Table 1 summarises their baseline characteristics.

Clinical outcome

Echocardiography was carried out at a median of 36 days after AMI (range 25–51). Twenty-two patients (11.6%) suffered cardiac death within 36 days. Of the 168 patients who died follow-up of 167 (99.4%) attended for echocardiographic examination and satisfactory images were obtained in 160. Table 2 gives the geometric means for LV dimensions and LVEF. Nearly 41% of those with a satisfactory echo image had an LVEF below 0.4. Mortality was 11% for men and 12.5% for women (p = NS); 20.8% for patients > 75 years p 10.2% for patients ≤ 75 year (p = 0.13); 13.1% for anterior MI p 10.2% for inferior MI.
Change in ST segment elevation

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(p = NS); 42.9% for patients with diabetes mellitus v 9.2% for patients without (p < 0.002); 15.6% for patients with hypertension v 10.9% for patients without (p = NS). Smokers were at lower risk: smoker mortality (3.4%) v previous smokers (11.4%) v non-smokers (24.2%; p = 0.001). Although deaths that could not be attributed to a cardiac cause were excluded inclusion of these deaths in the analysis did not affect the statistically significant association between ST segment change and clinical outcome.

### Table 2 Clinical outcome up to 36 days

<table>
<thead>
<tr>
<th></th>
<th>Anterior MI</th>
<th>Inferior MI</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac mortality (%)</td>
<td>11 (13)</td>
<td>9 (10)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Reinfarction (%)</td>
<td>4 (4)</td>
<td>8 (9)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>36.9 (22.6–60.1)</td>
<td>29.3 (20.6–41.7)***</td>
<td>32.8 (21.0–51.2)</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>61.8 (44.4–86.1)</td>
<td>53.6 (39.9–72.0)*</td>
<td>57.5 (41.7–79.4)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.38 (0.27–0.53)</td>
<td>0.44 (0.35–0.55)*</td>
<td>0.42 (0.30–0.55)</td>
</tr>
<tr>
<td>LVEF &lt; 0.40 (%)</td>
<td>43/82 (52)</td>
<td>22/76 (29)**</td>
<td>65/158 (41)</td>
</tr>
<tr>
<td>Cardiac mortality or LVEF &lt; 0.40 (%)</td>
<td>56/95 (59)</td>
<td>31/85 (37)**</td>
<td>87/180 (48)</td>
</tr>
</tbody>
</table>

*p < 0.02, **p < 0.005, ***p < 0.001.

LVESVI, left ventricular end systolic volume index; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction.

LVESVI and LVEDVI shown as geometric mean (geometric SD).

### Table 3 Relation between achieving a 50% resolution in ST elevation and 36 day clinical outcome

<table>
<thead>
<tr>
<th>Time</th>
<th>ST fall</th>
<th>Cardiac mortality (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 day cardiac mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>≥ 50%</td>
<td>1/77</td>
<td>1.3*</td>
<td>95.2</td>
<td>45.8</td>
<td>18.2</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>20/110</td>
<td>18.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>≥ 50%</td>
<td>4/88</td>
<td>4.5</td>
<td>80.0</td>
<td>51.2</td>
<td>16.7</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>16/96</td>
<td>16.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>≥ 50%</td>
<td>3/109</td>
<td>2.8*</td>
<td>83.3</td>
<td>65.0</td>
<td>20.8</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>15/72</td>
<td>20.8</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion with left ventricular ejection fraction < 0.40

<table>
<thead>
<tr>
<th>Time</th>
<th>ST fall</th>
<th>LVEF &lt; 0.40 (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 min</td>
<td>≥ 50%</td>
<td>16/72</td>
<td>31.7*</td>
<td>75.0</td>
<td>59.6</td>
<td>55.8</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>48/86</td>
<td>55.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>≥ 50%</td>
<td>21/80</td>
<td>26.3*</td>
<td>66.7</td>
<td>63.4</td>
<td>55.3</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>42/76</td>
<td>55.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>≥ 50%</td>
<td>35/102</td>
<td>34.3**</td>
<td>45.3</td>
<td>73.6</td>
<td>54.7</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>8/93</td>
<td>54.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.001; **p < 0.01.

PPV, positive predictive value; NPV, negative predictive value.

### Figures

**Figure 1** Resolution of ST elevation in anterior and inferior MI within 180 minutes of initiating thrombolysis.

**Table 3** shows the relation between 50% resolution of ST elevation and cardiac mortality and LVEF < 0.4. Patients with 50% resolution of ST segment in the lead of maximal ST elevation by 60, 90 or 180 minutes experienced lower cardiac mortality by 36 days than those with persistent ST elevation. This was also seen in sum ST analysis. The 60 minute maximal lead ECG predicted cardiac death with the highest sensitivity (95.2%) and negative predictive value (98.7%) but with low specificity (45.8%). Sum ST elevation predicted cardiac mortality but with lower sensitivity, specificity, positive and negative predictive values compared with the equivalent maximal lead measurement (data not shown). A 50% decrease in maximal lead ST elevation identified patients with a lower prevalence of LVEF < 0.4 at 36 days. The 60 minute ECG had the highest sensitivity for this clinical outcome. Sum ST and maximum lead ST data were essentially equivalent (60 minutes sum ST data 78% sensitivity and 46% specificity for LVEF < 0.40).

A clear relation between the resolution of ST elevation and LV volume and function was seen (table 4). Resolution of ST elevation was associated with higher LVEF, smaller LVESVI, and smaller LVEDVI compared with persistent ST elevation. This suggests that greatest preservation of LV function is achieved by the earliest reperfusion.

### Analysis according to infarct site

Failure of maximal lead ST segment elevation to resolve by 60, 90 or 180 minutes after onset of thrombolysis was associated with a significantly higher mortality at 36 days (fig 2). Significant differences persist to the 180 minute ECG for anterior MI but not for inferior MI. Larger LV volume (LVESVI and LVEDVI) and lower LVEF in anterior MI were associated with persisting ST elevation at 60 and 90 minutes (table 4) but only for LVESVI.
at 180 minutes. This was true for maximal lead and sum ST elevation but more statistically consistent results were obtained from analysis of maximal lead measurements. Persistent ST elevation at 60, 90 or 180 minutes was not associated with significantly lower LVEF or larger volumes in those patients with inferior MI.

RECEIVER OPERATING CHARACTERISTIC CURVES AND CLINICAL OUTCOME

ROC curves are shown for the prediction of cardiac death and LVEF < 0.4 based upon the lead of maximum ST elevation (fig 3) for each ECG time. There was no statistically significant difference between the areas under the ROC curves for the three ECG times. Similar findings occurred with data from sum ST leads for each time point: the area under ROC curves for cardiac mortality was 0.707 for 60 minute ECG, 0.718 for 90 minute ECG, and 0.665 for 180 minute ECG. For predicting LVEF < 0.4 area under ROC curve was 0.657 at 60 minutes, 0.626 at 90 minutes, 0.619 at 180 minutes. The 60 minute ECG, therefore, performs at least as well in ROC analysis as later ECGs and maximal lead at least as well as sum ST elevation in predicting cardiac mortality and LVEF < 0.4 after thrombolysis.

RESPONSE TO THROMBOLYSIS ACCORDING TO PRESENTATION TIME

Time to thrombolysis influenced the proportion of patients achieving a 50% decrease in ST segment elevation at each time point. Comparing the proportions achieving a 50%
decrease in ST segment elevation by pain to
needletimes (PTN) values were: for 60 minute
ECG proportion achieving a 50% decrease in
single lead ST segment elevation was 46% for
PTN of < 4 hours, 28% for PTN of > 4 hours
(p < 0.05), 13% for PTN of > 6 hours
(p < 0.05 v < 4 or < 6 hours). For 90 minute
ECG proportion achieving a 50% decrease in
single lead ST segment elevation was 55% for
PTN of < 4 hours, 26% for PTN of > 4 hours
(p < 0.05), 17% for PTN of > 6 hours
(p < 0.05 v < 4 or < 6 hours). For 180 minute
ECG proportion achieving a 50% decrease in
single lead ST segment elevation was 66% for
PTN of < 4 hours, 46% for PTN of > 4 hours
(p < 0.05), 24% for PTN of > 6 hours
(p < 0.05 v < 4 or < 6 hours).

Discussion
This study is the first to prospectively and
comparatively assess the predictive accuracy of
very early (60 minute) standard 12-lead ECGs
against post-infarction clinical end points and
later ECGs.

POPULATION STUDIED
In this unselected, consecutive series of patients
the use of thrombolysis, median symptom to
treatment time, and presentation to treatment
time was comparable to GUSTO7 and ISIS-418
but cardiac mortality and overall mortality were
higher. Mortality in this study was typical of
unfiltered patients21 rather than those selected
for trials. This study is therefore a more valid
assessment of the predictive value of ST
segment change in routine practice than previ-
ous studies, which tended to be small7 9 10 16 or
based on patients in thrombolytic and coronary
intervention trials.8 11 12 19

The higher than expected mortality in the
inferior MI group (10.2%) may be because
85% of inferior MI in this study had poor
prognostic ECG features, such as ST elevation
in the lateral chest leads (47%) or precordial
ST depression (66%) (28% have both), on
their admission ECG, which suggests a high
prevalence of multi-vessel coronary disease.17
This may also explain the high overall mortality
and the high prevalence of LVEF < 0.40 at 36
days compared with earlier studies, for example
GISSI-2.11 Low cardiac mortality was seen in
current smokers in this study compared with
ex-smokers and non-smokers. This has been
observed before29 30 but remains incompletely
explained.

ECG CRITERIA FOR SUCCESSFUL THROMBOLYSIS
Three previous studies have shown a positive
association between early (three to four hours)
resolution of sum ST segment elevation and
lower mortality and higher LV function.11–13
Unfortunately almost half the total deaths had
occurred before the study ECG was recorded.
In this study four patients died despite a 50%
decrease in ST elevation by 90 minutes in the
lead of maximum ST elevation. Of these two
suffered re-infarction and one re-elevation of
ST segment on the 180 minute ECG. This is
not surprising as ST resolution suggests
restored vessel patency, which then has the
potential to become re-occluded. Although
continuous ST segment monitoring may detect
fluctuations in ST elevation soon after throm-
bolysis that could be missed on standard
ECGs7 8 11 the strong association between
standard ECG measurements and clinical out-
come in this study suggests this did not signifi-
cantly interfere with the present analysis.

PREDICTION OF OUTCOME BY INFARCT
Site ST segment resolution predicted cardiac
mortality and LV function after anterior MI
but only the 60 minute ECG was associated
with cardiac mortality after inferior MI. This
result is also consistent with the theory that
reperfusion within the first 60 minutes is
particularly important although the lack of sta-
tistical significance in mortality data from the
90 and 180 minute ECGs may be a type 2 sta-
tistical error.

LVEF after inferior MI was significantly bet-
ter than after anterior MI and LV volumes were
smaller. No association was seen after inferior
MI between ST resolution and LV size and
function. Previous studies do not give consist-
ent results on this point.12 26

Generally inferior MI may jeopardise less
myocardium than anterior MI but in this study
there were also fewer patients with anterior MI
who achieved 50% ST resolution at 60 and 90
minutes compared with inferior MI. This was also observed in the ISAM and INJECT studies, which suggests that thrombolysis may be less effective in anterior than inferior MI. For streptokinase treatment this may relate to fibrinolysis itself because fewer patients with anterior MI achieved a systemic fibrinolytic state 60 minutes after streptokinase (fibrinogen < 0.4 g/dl) than patients with inferior MI: 59.5% compared with 76.1% (p < 0.05).

RECEIVER OPERATING CHARACTERISTIC CURVES

The ROC curve is a useful method of evaluating and comparing the accuracy of prognostic markers. We used a method of comparison that corrected for the correlation between ECGs recorded at different times on the same patient. The area under the ROC curve is the proportion of correct predictions of a specified outcome that would be made using the prognostic marker being assessed. For example, in this study cardiac death would be correctly predicted by the 60 minute maximal lead analysis in 73% of cases. There was no statistically significant difference between the ROC areas derived from our data and we calculate that more than 2000 patients would be required to detect a difference between these areas at 5% significance with 80% power. This supports our hypothesis that the 60 minute ECG is at least as accurate in predicting clinical outcome as later ECGs. In addition we would recommend maximal lead ST measurement over sum ST measurement as it has equal or better accuracy in predicting outcome and is simpler to use.

PREDICTION OF OUTCOME—SENSITIVITY AND SPECIFICITY

When constructing a ROC curve multiple values of ST segment are plotted but in practice it is probable that only one will be used to separate patients into prognostic groups. Sensitivity and specificity of that value must then be considered. There is a reciprocal relation between sensitivity and specificity for outcome prediction at the different ECG times. Sensitivity is highest for the earliest ECG and decreases with time whereas the specificity increases. Sensitivity and specificity also vary depending on the ST elevation cut off point chosen—as the cut off point increases so does the sensitivity of predicting a poor outcome while the specificity decreases. This is also true for other studies. Furthermore the number of patients who reperfused (achieving 50% ST resolution) increases with time. Therefore to identify the maximum number of patients at high risk an early ECG with high cut off point (that is, a large % fall in ST segment elevation) should be chosen but this has the disadvantage of low specificity. In this study 41% achieve a 50% decrease in ST elevation in the lead of maximum ST elevation by 60 minutes and have a 36 day mortality of only 1.3%. This leaves 59% of patients identified as high risk. A later ECG could be taken to identify smaller group of patients at higher risk (at 180 minutes 40% of patients have ST elevation > 50% of baseline with 20.8% cardiac mortality) but some high risk patients will be missed and the opportunity for successful rescue treatment may be diminishing, indeed some patients may already have died. A lower cut off point could be taken at 60 minutes, for example in our study, 20% of patients failed to achieve any decrease in maximal lead ST elevation. Their mortality was 27% compared with 7% among those with some degree of ST decrease (p < 0.001).

CONCLUSIONS

Using simple measurements of ST segment elevation we were able to identify high and low risk groups of patients as early as 60 minutes after initiating thrombolysis in an unselected group of patients with first AMI. The 60 minute ECG predicted outcome as well as later ECGs in ROC curve analysis. Single lead data proved a simple and universally applicable marker that could predict outcome at least as accurately as more time consuming measurements of sum ST changes. The 60 minute ECG prediction of clinical outcome emphasises the importance of early reperfusion and identifies high risk patients who may benefit from rescue reperfusion therapy. Patients in whom there is failure of ST segment elevation to decrease at all by 60 minutes and patients who reinfarct after early ST segment resolution seem to warrant the most aggressive treatment.

We are very grateful for the support and encouragement of all hospital staff and patients involved in this work.


