Intravenous thrombolysis plus aspirin is the most widely used treatment for patients presenting in the acute phase of myocardial infarction. Thrombolytic treatment prevents approximately 20–30 deaths per 1000 patients treated, with a proportional reduction in mortality of up to 25% in certain subgroups. However, thrombolysis is not always successful. In the angiographic substudy of the GUSTO-I trial, the 90 minute arterial patency rate (defined by the presence of TIMI grade 2 or 3 flow) was 54% in patients who received streptokinase, with only 29% of patients having desirable TIMI grade 3 flow. Streptokinase, with only 29% of patients having desirable TIMI grade 3 flow.

Failure of thrombolysis by streptokinase: detection with a simple electrocardiographic method

A G C Sutton, P G Campbell, D J A Price, E D Grech, J A Hall, A Davies, M J Stewart, M A de Belder

Abstract

Objective—To determine whether simple, readily applicable ECG criteria will allow early prediction of inadequate (< TIMI 3) flow in the infarct related vessel in patients receiving thrombolytic treatment for acute myocardial infarction; and to determine the success of streptokinase in achieving adequate antegrade flow in the infarct related vessel two hours after starting treatment.

Design—Cohort study.

Setting—Regional cardiothoracic unit.

Patients—100 sequential patients with acute myocardial infarction.

Interventions—Coronary angiography two hours after the initiation of thrombolytic treatment, proceeding to rescue angioplasty for inadequate flow in the infarct related vessel where appropriate.

Main outcome measures—Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of six ECG criteria for the detection of inadequate antegrade flow in the infarct related vessel.

Results—The ECG test that performed best as a positive test for < TIMI 3 flow in the infarct related vessel was < 50% resolution of the ST segment elevation in the worst lead and no accelerated idioventricular rhythm. This had a sensitivity of 81%, specificity of 88%, positive predictive value of 87%, negative predictive value of 83%, and overall accuracy of 85%.

Conclusions—Sensitive, specific, and simple ECG criteria are defined for diagnosing failure of thrombolytic treatment with streptokinase. These allow the early detection of patients at high risk of further adverse events from a persistently occluded vessel. They may be used without recourse to sophisticated equipment or complex analyses. Such patients can then be considered for alternative treatments or enrolment into appropriate research protocols.

(Heart 2000;84:149–156)

Keywords: myocardial infarction; thrombolysis; streptokinase

Intravenous thrombolysis plus aspirin is the most widely used treatment for patients presenting in the acute phase of myocardial infarction. Thrombolytic treatment prevents approximately 20–30 deaths per 1000 patients treated, with a proportional reduction in mortality of up to 25% in certain subgroups. However, thrombolysis is not always successful. In the angiographic substudy of the GUSTO-I trial, the 90 minute arterial patency rate (defined by the presence of TIMI grade 2 or 3 flow) was 54% in patients who received streptokinase, with only 29% of patients having desirable TIMI grade 3 flow.

Accelerated tissue plasminogen activator, the thrombolytic regimen that yields superior early flow rates, still produced TIMI 3 flow in only 54% of patients. Failure to achieve arterial patency following thrombolytic treatment is associated with a poor outcome. Therefore, simple non-invasive methods are desirable in order to detect patients with failed thrombolysis at an early stage, so that alternative strategies can be considered before irreversible myocardial necrosis occurs. Alternative methods include the repeated use of thrombolytic agents, rescue angioplasty, or even emergency coronary artery bypass surgery.

Several studies have examined the use of specific ECG criteria as markers of inadequate arterial flow in the infarct related vessel, but many have design flaws and others describe methods that are currently impractical in busy coronary care units (CCUs).

The objectives of this study were to correlate the findings at coronary angiography with the ECG findings two hours after the onset of thrombolytic treatment in order to determine whether simple ECG formulae could be used to identify patients with persistent arterial occlusion prospectively and non-invasively. A further objective was to assess the efficacy of thrombolytic treatment in these patients.

Methods

Over a 14 month period starting in August 1997, a consecutive series of 100 patients presenting to our CCU within 10 hours of the onset of acute myocardial infarction was studied. Acute myocardial infarction was identified by the onset of typical chest pain lasting more than 30 minutes, unrelieved by sublingual nitrate, and associated with typical ST segment elevation on the standard 12 lead ECG.

The following factors were exclusion criteria: cardiogenic shock; contraindication to thrombolysis; confounding features on the pretreatment ECG (for example, bundle branch block); no femoral arterial access; pregnancy; inability to give fully informed consent.
Absolute contraindications to thrombolysis in this study were: active bleeding; gastrointestinal bleeding within the last three months; uncontrolled hypertension (systolic blood pressure of greater than 200 mm Hg on repeated measurement); any history of coagulopathy or bleeding diathesis, including warfarin treatment; cerebrovascular accident within the last six months; any previous history of confirmed intracerebral haemorrhage; major surgery or significant trauma within the last 10 days, including prolonged cardiopulmonary resuscitation; and proliferative (but not background) diabetic retinopathy.

The local ethics committee approved the study. All patients gave informed and written consent.

**DRUG ADMINISTRATION**

Streptokinase was given in the standard dose of 1.5 x 10⁶ units over 60 minutes. All patients except one received aspirin. Other drug treatment was prescribed at the discretion of the attending cardiologist.

**ECG ANALYSIS**

An ECG was recorded just before starting the streptokinase infusion and immediately before coronary angiography two hours later. The second ECG was recorded immediately before coronary angiography in the cardiac catheterisation laboratory. The following measurements on each ECG were recorded: ST segment elevation in the lead with the maximum ST segment elevation (“worst lead”) before thrombolytic treatment; the summed ST segment elevation in all leads reflecting the infarct zone; the peak of the T wave in the worst lead; the summed peaks of the T waves in all leads reflecting the infarct zone; and the presence of an accelerated idioventricular rhythm on the two hour ECG. ST segments were analysed 80 ms after the J point. Six ECG criteria were used to predict inadequate flow in the infarct related vessel. Inadequate flow was defined first by < TIMI 3 flow, and second by < TIMI 2 flow. The criteria used are shown below.

1. Less than 50% resolution of the ST segment elevation in the worst lead and no accelerated idioventricular rhythm two hours after the initiation of thrombolytic treatment.
2. Less than 70% resolution of the ST segment elevation in the worst lead and no accelerated idioventricular rhythm two hours after the initiation of thrombolytic treatment.
3. Less than 30% resolution of the ST segment elevation in the worst lead and no accelerated idioventricular rhythm two hours after the initiation of thrombolytic treatment.

**COMORBIDITIES**

- Hypertension 22
- Diabetes 8
- Hypercholesterolaemia* 75

**CORONARY ANGIOGRAM ANALYSIS**

Coronary angiography was performed through the right femoral artery two hours after the initiation of thrombolytic treatment. Flow in the infarct related vessel was quantified according to the TIMI classification4 (table 1).

<table>
<thead>
<tr>
<th>Grade of TIMI flow</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Complete occlusion</td>
</tr>
<tr>
<td>1</td>
<td>Penetration without perfusion. Coronary bed distal to the occlusion failure</td>
</tr>
<tr>
<td>2</td>
<td>Partial perfusion. Full but slow opacification of the coronary bed distal to the occlusion</td>
</tr>
<tr>
<td>3</td>
<td>Complete perfusion</td>
</tr>
</tbody>
</table>

TIMI, thrombolysis in myocardial infarction trial.

The ECG criteria were selected following a review of published reports, with particular emphasis on criteria that could be measured quickly and without recourse to specialised equipment. All the prespecified criteria were measured in all the patients where possible, and we tested no other criteria apart from those described here.

**STATISTICAL METHODS**

The aim of the diagnostic method was the detection of failure of thrombolysis, defined by the presence of < TIMI grade 3 flow in the infarct related vessel. Accordingly, the specificity of the test is a measure of the ability of the test to detect genuine cases of failed reperfusion (that is, the number of cases with failed reperfusion on ECG and at angiography, as a proportion of all cases of failed reperfusion at angiography). The specificity of the test is a measure of the ability of the test to detect genuine cases of successful reperfusion (that is, the number of cases with successful reperfusion detected by the ECG criteria and at angiography, as a proportion of all cases of successful reperfusion at angiography). The positive predictive value (PPV) is the proportion of patients with a positive ECG test who have failed reperfusion at angiography. The negative predictive value (NPV) is the proportion of patients with a negative ECG test who have successful reperfusion at coronary angiography.

**Table 1** TIMI flow in the infarct related vessel

<table>
<thead>
<tr>
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<td>3</td>
<td>Complete perfusion</td>
</tr>
</tbody>
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**Table 2** Demographic details of enrolled patients

<table>
<thead>
<tr>
<th>Number (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Ex-smoker</td>
</tr>
<tr>
<td>Hypercholesterolaemia*</td>
</tr>
</tbody>
</table>

*Defined by a random cholesterol on admission of > 5.2 mmol/l or if the patient was taking a lipid lowering agent.
Failure of thrombolysis by streptokinase

Table 3 - Numbers of patients fulfilling positive (test +) and negative (test −) ECG criteria with < TIMI 3 or TIMI 3 flow in the infarct related vessel

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Test +</th>
<th>Test −</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39 (RCA 19, LAD 15)</td>
<td>6 (RCA 3, LAD 3)</td>
</tr>
<tr>
<td>2</td>
<td>44 (RCA 22, LAD 17)</td>
<td>19 (RCA 9, LAD 7)</td>
</tr>
<tr>
<td>3</td>
<td>33 (RCA 16, LAD 12)</td>
<td>6 (RCA 3, LAD 3)</td>
</tr>
<tr>
<td>4</td>
<td>38 (RCA 21, LAD 12)</td>
<td>11 (RCA 5, LAD 4)</td>
</tr>
<tr>
<td>5</td>
<td>39 (RCA 20, LAD 14)</td>
<td>9 (RCA 5, LAD 4)</td>
</tr>
<tr>
<td>6</td>
<td>42 (RCA 21, LAD 15)</td>
<td>11 (RCA 5, LAD 3)</td>
</tr>
</tbody>
</table>

Table 4 - Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each ECG test as a proportion of the whole study group.

| ECG Criteria for Inadequate Antegrade Flow and Findings at Coronary Angiography |

Table 3 shows the numbers of patients fulfilling each of the ECG criteria for inadequate (< TIMI 3) antegrade flow or adequate (TIMI 3) flow, together with the grade of TIMI flow at angiography. Shown in brackets are the equivalent numbers for patients with the right coronary artery and the left anterior descending coronary artery as the infarct related vessel.

Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of all the ECG criteria for inadequate antegrade flow, defined by < TIMI 3 flow. Values for the left anterior descending coronary artery and right coronary artery as the infarct related vessel are also shown. The only ECG test for detecting < TIMI 3 flow with a sensitivity, specificity, and overall accuracy of 85% is the one with a positive predictive value of 83% and a negative predictive value of 85%.

Table 4 - Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each ECG test as a proportion of the whole study group.

<table>
<thead>
<tr>
<th>Positive test for &lt; TIMI 3 flow</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>81 (RCA 76)</td>
<td>88 (RCA 86)</td>
<td>87 (RCA 86)</td>
<td>83 (RCA 75)</td>
<td>85 (RCA 80)</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>92 (RCA 88)</td>
<td>63 (RCA 57)</td>
<td>70 (RCA 71)</td>
<td>89 (RCA 80)</td>
<td>77 (RCA 74)</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>69 (RCA 64)</td>
<td>88 (RCA 86)</td>
<td>85 (RCA 84)</td>
<td>75 (RCA 67)</td>
<td>79 (RCA 74)</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>79 (RCA 84)</td>
<td>78 (RCA 76)</td>
<td>78 (RCA 81)</td>
<td>80 (RCA 80)</td>
<td>79 (RCA 80)</td>
</tr>
<tr>
<td>Criterion 5</td>
<td>81 (RCA 80)</td>
<td>82 (RCA 76)</td>
<td>81 (RCA 80)</td>
<td>82 (RCA 76)</td>
<td>82 (RCA 78)</td>
</tr>
<tr>
<td>Criterion 6</td>
<td>88 (RCA 84)</td>
<td>78 (RCA 76)</td>
<td>79 (RCA 81)</td>
<td>87 (RCA 80)</td>
<td>83 (RCA 80)</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; NPV, negative predictive value; PPV, positive predictive value; RCA, right coronary artery.
positive predictive value, negative predictive value, and accuracy all > 80% was < 50% ST segment resolution in the worst lead and no accelerated idioventricular rhythm on the two hour ECG (that is, criterion 1). This measurement of the ST segment was also the easiest to perform.

We also looked at the numbers of patients fulfilling each of the ECG criteria for inadequate antegrade flow, with their angiographic findings, when inadequate antegrade flow was defined as < TIMI 2 flow (table 5). There were fewer false negative results and more false positive results for all ECG criteria with this definition of inadequate antegrade flow. Therefore the same ECG criteria have improved sensitivity and negative predictive values for < TIMI 2 flow, but at the expense of a reduction in specificity and positive predictive value (table 6).

Analyses of patients with the left anterior descending coronary artery and right coronary artery as the infarct related vessel are interpreted with caution given the small numbers, but show that the sensitivity and negative predictive value of our best ECG test for < TIMI 3 are superior for patients with acute myocardial infarction in the left anterior descending territory than in the right coronary territory. Considering TIMI 3 flow as adequate antegrade flow (table 3), there were 24 patients with the right coronary artery as the infarct related vessel in whom the ECG test was negative, but six of these patients (25%) had a falsely negative test. Among patients with the left anterior descending coronary artery as the infarct related vessel, 19 had a negative ECG test, but this was falsely negative in just two (11%).

### Table 5
Numbers of patients fulfilling positive (test +) and negative (test −) ECG criteria with < TIMI 2 or TIMI 2 flow in the infarct related vessel

<table>
<thead>
<tr>
<th>Criterion</th>
<th>TIMI &lt;2</th>
<th>TIMI 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>32 (RCA 18, LAD 12)</td>
<td>13 (RCA 4, LAD 6)</td>
</tr>
<tr>
<td>Test −</td>
<td>4 (RCA 3, LAD 0)</td>
<td>50 (RCA 21, LAD 19)</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>Test +</td>
<td>34 (RCA 20, LAD 12)</td>
</tr>
<tr>
<td>Test −</td>
<td>2 (RCA 1, LAD 0)</td>
<td>34 (RCA 14, LAD 13)</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>Test +</td>
<td>28 (RCA 15, LAD 11)</td>
</tr>
<tr>
<td>Test −</td>
<td>8 (RCA 6, LAD 1)</td>
<td>52 (RCA 21, LAD 21)</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>Test +</td>
<td>33 (RCA 20, LAD 10)</td>
</tr>
<tr>
<td>Test −</td>
<td>3 (RCA 1, LAD 2)</td>
<td>47 (RCA 19, LAD 19)</td>
</tr>
<tr>
<td>Criterion 5</td>
<td>Test +</td>
<td>32 (RCA 18, LAD 12)</td>
</tr>
<tr>
<td>Test −</td>
<td>4 (RCA 3, LAD 0)</td>
<td>47 (RCA 18, LAD 20)</td>
</tr>
<tr>
<td>Criterion 6</td>
<td>Test +</td>
<td>35 (RCA 20, LAD 12)</td>
</tr>
<tr>
<td>Test −</td>
<td>1 (RCA 1, LAD 0)</td>
<td>45 (RCA 19, LAD 19)</td>
</tr>
</tbody>
</table>

n = 99 (one patient excluded because of left bundle block at two hours).

### Table 6
Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each ECG test as a marker for < TIMI 2 flow

<table>
<thead>
<tr>
<th>Positive test for &lt; TIMI 2 flow</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>89 (RCA 86)</td>
<td>79 (RCA 84)</td>
<td>71 (RCA 82)</td>
<td>93 (RCA 88)</td>
<td>83 (RCA 80)</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>94 (RCA 95)</td>
<td>54 (RCA 56)</td>
<td>54 (RCA 65)</td>
<td>94 (RCA 93)</td>
<td>69 (RCA 74)</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>78 (RCA 71)</td>
<td>83 (RCA 84)</td>
<td>72 (RCA 79)</td>
<td>87 (RCA 78)</td>
<td>81 (RCA 78)</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>72 (RCA 76)</td>
<td>67 (RCA 77)</td>
<td>94 (RCA 95)</td>
<td>81 (RCA 85)</td>
<td>78 (RCA 78)</td>
</tr>
<tr>
<td>Criterion 5</td>
<td>89 (RCA 86)</td>
<td>75 (RCA 72)</td>
<td>67 (RCA 72)</td>
<td>92 (RCA 86)</td>
<td>80 (RCA 78)</td>
</tr>
<tr>
<td>Criterion 6</td>
<td>97 (RCA 95)</td>
<td>71 (RCA 76)</td>
<td>66 (RCA 77)</td>
<td>98 (RCA 95)</td>
<td>81 (RCA 85)</td>
</tr>
</tbody>
</table>

RESCUE ANGIOPLASTY AND OUTCOME

The flow in the infarct related vessel is shown in table 7. Fifty two patients had TIMI 3 flow on the first injection of contrast. A further seven patients achieved TIMI 3 flow by the end of the diagnostic angiogram. One of the 52 patients with initial TIMI 3 flow underwent percutaneous transluminal coronary angioplasty (PTCA) because the severity of the underlying coronary artery stenosis was considered highly likely to lead to reinfarction, but the other 58 patients with TIMI 3 flow by the end of the procedure did not undergo PTCA.

Of the 41 patients without TIMI 3 flow by the end of the coronary angiogram, rescue angioplasty was attempted on 36 occasions. In this group, final flow in the infarct related vessel was TIMI 3 in 30 patients, TIMI 2 in two, TIMI 1 in one, and TIMI 0 in three. Rescue angioplasty was not attempted in five patients: one patient with TIMI 2 flow but who was pain free and allergic to aspirin; one patient with an occluded vessel who was 12 hours into the myocardial infarction at the time of the diagnostic catheter and who was pain free and haemodynamically stable; one patient with severe triple vessel disease in whom the infarct related vessel could not be identified with certainty (but retrospectively was felt to be the circumflex artery); one patient with a proximally occluded right coronary artery but who was pain free and had evidence of collateral filling to the distal vessel; and one patient who was pain free with TIMI 2 flow and unfavourable anatomy for intervention.

Of the 52 patients who had TIMI 3 flow at the first contrast injection, six (11.5%) sustained reinfarction requiring repeat coronary angiography and angioplasty during the same hospital admission; four required repeat coronary angiography proceeding to angioplasty for postinfarct angina; and two patients who had been discharged re-presented within 10 days of the original presentation with reinfarction and unfavourable anatomy for intervention. Four patients were treated by coronary angioplasty to the coronary artery lesion identified on the original diagnostic angiogram. One of the 52 patients with initial TIMI 3 flow following thrombolytic treatment (23.1%) required intervention for reinfarction or postinfarct angina within 10 days of the original presentation. Among the group leaving the cardiac catheter laboratory with TIMI 3 flow after angiography (59), there were three additional patients who reinfarcted during the hospital admission. Thus the reinfarction rate or requirement for clinically driven PTCA among the group with TIMI 3 flow following coronary angiography alone was 15 of
Failure of thrombolysis by streptokinase

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that ST segment resolution is seen with reper-
creased mortality following acute myocardial
thrombolysis), which is associated with in-
grade flow in the infarct related vessel (failed
The aim of this study was to see whether a uni-
DETECTION OF FAILED REPERFUSION
PREVIOUSLY DESCRIBED ECG CRITERIA FOR
postinfarction angina within 10 days.
that achieved following thrombolysis alone sus-
angiographic evidence of TIMI 3 flow was
for in-hospital mortality among the patients with initial TIMI 3 flow (52) was 3.8% and for those achieving TIMI 3 flow by the end of the procedure (59), 3.4%. Among the patients with < TIMI 3 flow at initial angiography (48), the in-hospital mortality was 12.5%. Among those with < TIMI 3 flow after angiography (41), the in-hospital mortality was 14.6% (of the five patients not offered a rescue angioplasty, two died; of the 36 offered a rescue angioplasty, four died). The in-hospital mortality rate for the whole cohort was 8%.

Discussion
LIMITATIONS OF THROMBOLYTIC TREATMENT
This study confirms the limitations of throm-
bolytic treatment. Not only did 48% of our
patients fail to achieve the desired TIMI 3 flow
during catheter laboratory procedure
Flow at catheter laboratory procedure
(including intervention if performed)

| Flow at first | Flow after | Flow at end of |
| contrast | completion | laboratory procedure |
| injection | of angiogram | (including intervention if performed) |
| TIMI 0 | 35 | 31 | 5 |
| TIMI 1 | 1 | 1 |
| TIMI 2 | 12 | 9 | 5 |
| TIMI 3 | 52 | 59 | 89 |

59 (25.4%). There were no deaths among these
15 patients.

Among the whole cohort of patients, six
underwent coronary artery bypass grafting
(CABG) before discharge. The in-hospital
mortality among the patients with initial TIMI 3 flow (52) was 3.8% and for those achieving TIMI 3 flow by the end of the procedure (59), 3.4%. Among the patients with < TIMI 3 flow at initial angiography (48), the in-hospital mortality was 12.5%. Among those with < TIMI 3 flow after angiography (41), the in-hospital mortality was 14.6% (of the five patients not offered a rescue angioplasty, two died; of the 36 offered a rescue angioplasty, four died). The in-hospital mortality rate for the whole cohort was 8%.

PREVIOUSLY DESCRIBED ECG CRITERIA FOR
DETECTION OF FAILED REPERFUSION
The aim of this study was to see whether a uni-
versally available and applicable ECG method
could identify patients with inadequate ante-
grade flow in the infarct related vessel (failed
thrombolysis), which is associated with in-
creased mortality following acute myocardial
infarction. It has been known for several years
that ST segment resolution is seen with reper-
fusion in the infarct related vessel, and several relatively complex electrocardiographic methods for the detection of failed reperfusion were described subsequently. However, the design of some of these studies is flawed. In addition, many of the techniques described are impractical because they require very frequent recording of static ECGs, continuous ST segment monitoring, or detailed analysis.

Some previous studies recording the degree of ST segment resolution apparent on two or more ECGs recorded at predetermined time intervals should be interpreted with caution, given that the final ECG assessment was performed after, not before, coronary
angiography. In our study, seven of 100 patients developed normal flow with the act of coronary angiography itself. Thus the very first angiographic appearances should be consid-
ered. In addition, the ECG that will be used to estimate antegrade flow should be performed immediately before angiography.

Other studies recording the degree of ST segment resolution on two or more ECGs recorded at predetermined time intervals cannot be relied upon for the assessment of early arterial patency because coronary angiography was performed many hours, or even days, after thrombolysis was given.

It seems logical that continuous ECG moni-
toring would be a superior technique to the
recording of static ECGs, and this technique
has been quite exhaustively investigated.
Veldkamp and colleagues reported that con-
tinuous ST segment monitoring was at least as
accurate as the most accurate of a number of
static electrocardiographic methods, and Zabel and colleagues found that the use of two
static ECGs before and two hours after throm-
bolytic treatment had the same predictive value
as continuous Holter monitoring with respect
to thrombolysis induced coronary artery
reperfusion. Some investigators have de-
scribed very specific and sensitive methods of
detecting arterial patency using continuous
ECG monitoring. For example, in a study of 38
patients Fernandez and colleagues reported
that ST segment reduction of 50% or more in
a single lead reflecting the infarct zone could
predict arterial patency 60 minutes after
thrombolysis with a sensitivity and specificity
of 96% and 94%, respectively. These investi-
gators showed that analysis of ST segment shift
during catheter laboratory procedure
Flow at end of
laboratory procedure
(including intervention if performed)

| Flow at end of |
| laboratory procedure |
| (including intervention if performed) |

| TIMI 0 | 35 | 31 | 5 |
| TIMI 1 | 1 | 1 |
| TIMI 2 | 12 | 9 | 5 |
| TIMI 3 | 52 | 59 | 89 |

TIMI 3 52 59 89
TIMI 2 12 9 5
TIMI 0 35 31 5

Among the whole cohort of patients, six
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but almost one quarter of patients in whom
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achieved following thrombolysis alone sus-
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postinfarction angina within 10 days.

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angiography. In our study, seven of 100 patients developed normal flow with the act of coronary angiography itself. Thus the very first angiographic appearances should be consid-
ered. In addition, the ECG that will be used to estimate antegrade flow should be performed immediately before angiography.

Other studies recording the degree of ST segment resolution on two or more ECGs recorded at predetermined time intervals cannot be relied upon for the assessment of early arterial patency because coronary angiography was performed many hours, or even days, after thrombolysis was given.

It seems logical that continuous ECG moni-
toring would be a superior technique to the
recording of static ECGs, and this technique
has been quite exhaustively investigated.

Veldkamp and colleagues reported that con-
tinuous ST segment monitoring was at least as
accurate as the most accurate of a number of
static electrocardiographic methods, and Zabel and colleagues found that the use of two
static ECGs before and two hours after throm-
bolytic treatment had the same predictive value
as continuous Holter monitoring with respect
to thrombolysis induced coronary artery
reperfusion. Some investigators have de-
scribed very specific and sensitive methods of
detecting arterial patency using continuous
ECG monitoring. For example, in a study of 38
patients Fernandez and colleagues reported
that ST segment reduction of 50% or more in
a single lead reflecting the infarct zone could
predict arterial patency 60 minutes after
thrombolysis with a sensitivity and specificity
of 96% and 94%, respectively. These investi-
gators showed that analysis of ST segment shift
during catheter laboratory procedure
Flow at end of
laboratory procedure
(including intervention if performed)

| Flow at end of |
| laboratory procedure |
| (including intervention if performed) |

| TIMI 0 | 35 | 31 | 5 |
| TIMI 1 | 1 | 1 |
| TIMI 2 | 12 | 9 | 5 |
| TIMI 3 | 52 | 59 | 89 |

TIMI 3 52 59 89
TIMI 2 12 9 5
TIMI 0 35 31 5

96% when the ST segment in the worst lead
was analysed. However, the same degree of ST
segment reduction by comparison with the ini-
tial ECG produced a sensitivity of just 64% for
TIMI 2 or 3 flow. It should be noted that
analysis of Holter recordings in that study was
performed retrospectively and not in real time,
which is essential for identifying patients who
may benefit from further intervention when
thrombolytic treatment has failed. Finally the
authors recommended that the non-invasive
prediction of arterial patency requires continu-
ous ST segment monitoring, or ECGs re-
corded at least as often as every 10 minutes,
and this is unlikely to be achieved in most
CCUs.

Other ECG techniques have also been
described. The use of the summed ST segment
elevation in all leads and measurement of the
degree of resolution has been reported to have
a high degree of sensitivity and specificity for
patency assessment. However, the measure-
ment of ST segment shift in all leads on a
standard 12 lead ECG is impractical, especially
as it requires measurement of small deviations
in leads which do not reflect the infarct zone.
CURRENT STUDY

In our study, we assessed the ability of several simple ECG criteria to detect inadequate flow in the infarct related vessel. The best ECG indicator for assessing the absence of TIMI 3 flow was failure of the ST segment elevation in the worst lead to fall by >50% in the absence of an accelerated idioventricular rhythm. This is also the simplest and most easily measured test among those we performed. We acknowledge that the sensitivity of this test for detecting flow less than TIMI 3 is not 100%, which is to be expected. In practice, this means that some patients with ST segment resolution might be incorrectly classified as having reperfused. There is evidence from a non-angiographic study\(^{21}\) that ST segment resolution as early as 60 minutes after the initiation of thrombolytic treatment identifies a low risk group of patients, even though it is reasonable to assume from our own study that some of these patients will not have normal antegrade flow in the infarct related vessel. This may occur in some patients if the infarct related vessel is well collateralised. Two of the nine patients in whom we incorrectly diagnosed successful reperfusion on the basis of ST segment resolution had detectable collateral flow to the distal bed of the occluded infarct related vessel, although collateral flow may have been present in the others but not angiographically detectable.

The failure of the ST segment elevation in the worst lead two hours after the initiation of thrombolysis to fall by \(\geq 50\%\) and the absence of accelerated idioventricular rhythm at this time is, however, a specific marker of inadequate (<TIMI 3) flow. Patients with these ECG features are highly likely to have either complete arterial occlusion or TIMI 1/TIMI 2 flow, and should be considered at high risk for further adverse cardiac events.

The sensitivity and negative predictive values of all our ECG tests are improved by considering adequate antegrade flow as either TIMI 2 or TIMI 3 flow, but this is at the expense of a reduction in specificity and positive predictive value. In a study linking the GUSTO-1 angiographic substudy and mortality outcomes,\(^{22}\) the 30 day mortality for TIMI 2 flow at 90 minutes was intermediate between that of TIMI 0/1 flow and that of TIMI 3 flow, but TIMI 2 flow was not associated with a significant survival advantage compared with TIMI grade 0 or 1. However, these data should be interpreted with caution. First, a single angiogram does not take into account the dynamic nature of coronary flow, so patients with TIMI 2 flow may have gone on to develop TIMI 3 flow. Second, a larger study may have detected a significant mortality benefit with the presence of TIMI 2 flow compared with TIMI 0/1 flow. Perhaps this is why patency is often described as the presence of TIMI 2 or TIMI 3 flow. We have included data for TIMI 2 and TIMI 3 flow, but believe that an ECG rule which detects the presence or absence of TIMI 2 flow in patients with acute myocardial infarction is only useful in clinical practice if TIMI 2 flow reliably progresses to TIMI 3. As this has not yet been demonstrated, the detection of failure to achieve TIMI 3 flow best identifies the high risk patient.

Including the presence or absence of chest pain at the time of the two hour ECG would further affect the sensitivity and specificity of our ECG test. We did not include chest pain as a criterion for failed thrombolysis because in our experience TIMI 3 flow can be associated with a persistent ache, TIMI 0 flow can be pain free following opiates, and there is often difficulty in distinguishing ischaemic and peri-carditic pain in patients who present after six hours. The result of the test would also depend on whether positive ECG criteria and chest pain are required or just the presence of one of them.

Including all accelerated idioventricular rhythms occurring in the two hours following the initiation of thrombolysis may increase specificity of the ECG criteria used in this study. However, the sensitivity of the test is unlikely to be affected as it has previously been reported that the absence of accelerated idioventricular rhythm does not indicate persistent arterial occlusion.\(^{23}\) In practice, only a small number of patients (just two in our study) will have an accelerated idioventricular rhythm captured on the two hour ECG. However, we could not include all cases of post-thrombolysis accelerated idioventricular rhythm in this analysis because many such reperfusion arrhythmias are too slow to trigger rate alarms on the CCU and often go undetected by busy nursing staff.

STUDY LIMITATIONS

The recording of static ECGs does not allow one to predict whether persistent ST segment elevation on a later ECG is caused by failure of reperfusion or by reperfusion injury, which can result in gross ST segment elevation.\(^{24-26}\) Shah and colleagues showed that over 50% of patients have transient increases in ST segment shifts following acute myocardial infarction.

However, evidence from a study of unselected patients suggests that ST segment analysis on an ECG 60 minutes after the initiation of thrombolysis is just as capable of identifying high risk patients as ECGs at two or three hours.\(^{27}\) In this study, the 36 day mortality for patients with <50% resolution of the ST segment elevation in the worst lead was 18.2% at 60 minutes, 16.7% at 90 minutes, and...
Failure of thrombolysis by streptokinase

20.8% at 180 minutes. In future, this may precipitate a move towards additional treatment (for example, rescue angioplasty) as early as 60 minutes after thrombolytic treatment is deemed to have failed.

We chose a method based on the recording of two static ECGs two hours apart for three reasons. First, continuous ECG monitoring is not currently available in our CCU. Second, it is known that a significant number of patients reperfuse between the first and second hours after initiation of thrombolysis. By two hours, 52% of our patients had achieved TIMI 3 flow. In the angiographic study of GUSTO-1, just 29% of those receiving intravenous streptokinase and subcutaneous heparin had achieved TIMI 3 flow by 90 minutes. Therefore, a later ECG for the non-invasive assessment of antegrade flow is likely to prevent an excess number of unnecessary coronary angiograms. Third, the two hour ECG still allows a second intervention to take place, if this is considered appropriate, before irreversible myocardial necrosis occurs.

We did not look specifically at T wave inversion as a marker of normal antegrade flow, although this has previously been examined. However, that study used early T wave inversion (< 24 hours after the administration of thrombolytic treatment) as a marker of normal antegrade flow assessed angiographically within 72 hours of admission. Thus the results cannot be extrapolated to the detection of normal flow in an infarct related vessel within the first few hours after administration of thrombolytic treatment, at a stage when further intervention may prevent irreversible myocardial necrosis.

Finally, although our ECG method was designed to detect < TIMI 3 flow in the infarct related vessel, there is evidence to show that tissue perfusion at a cellular level may be abnormal despite the presence of TIMI 3 flow in this vessel. In clinical practice, persistent ST segment elevation may be seen following acute infarction angioplasty despite the restoration of normal flow in the epicardial vessel. It is possible that in the future more sophisticated techniques, such as contrast echocardiography, will allow prediction of reperfusion at the tissue level, rendering the degree of TIMI flow in the epicardial vessel and the ST segment changes on the ECG irrelevant. Until such time, recurrent occlusion as a marker of normal antegrade flow in the infarct related vessel. Our current strategy is to offer rescue angioplasty as soon as the two hour ECG suggests persistent arterial occlusion, but we accept that further trials are required to demonstrate the superiority of this approach over other treatment options for failed thrombolysis, such as repeat thrombolytic treatment.

CONCLUSIONS

The simple, widely applicable ECG criteria described in our study can be interpreted without recourse to specialised equipment and have an important role in detecting patients at high risk of persistent arterial occlusion following thrombolytic treatment. Even though there is a move towards primary angioplasty for the treatment of acute myocardial infarction, thrombolysis is still the mainstay of treatment in most centres, but there is no consensus of opinion about the management of those patients in whom thrombolytic treatment is unsuccessful. Non-invasive criteria to detect these patients will be required before trials can be performed. From our study, patients with < 50% resolution of the ST elevation in the worst lead and no accelerated idioventricular rhythm two hours after the initiation of thrombolytic treatment have an 87% chance that inadequate (< TIMI 3) flow is present in the infarct related vessel. It has been suggested that a one hour ECG can reliably detect a high risk group of patients, but whether rescue angioplasty is appropriate at that stage would depend on whether ST segment analysis can reliably predict flow in the infarct related vessel.


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Endomyocardial fibrosis associated with antiphospholipid syndrome

A 50 year old woman presented with axillary vein thrombosis and was diagnosed as having the antiphospholipid syndrome. The patient also had hypereosinophilia and developed features of severe right heart failure. A transthoracic echocardiogram revealed features characteristic of hypereosinophilic cardiomyopathy leading to endomyocardial fibrosis. Various cardiac manifestations associated with antiphospholipid syndrome have been reported, including dilated cardiomyopathy, mural thrombi, valvar heart disease, non-bacterial vegetations, and pericardial effusion. However, the association between endomyocardial fibrosis and antiphospholipid syndrome has not been reported before.

The apical four chamber transthoracic echocardiogram shows endomyocardial fibrosis. The infiltration has characteristically involved the apical segments of both right (RV) and left (LV) ventricles leading to virtual obliteration of the apices in systole (top, arrows). The right ventricle cavity is very small and the right atrium (RA) is very enlarged. The diastolic view (bottom) reveals tethering of the apical interventricular septum. The basal segment of the interventricular septum is bowing to the left ventricle because of the raised intracavity pressure in the right ventricle during diastole.

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Failure of thrombolysis by streptokinase: detection with a simple electrocardiographic method

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