Use of the maximal ST/HR slope to estimate myocardial ischaemia after recent myocardial infarction

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SUMMARY  Fifty two patients were examined 4–6 weeks after myocardial infarction to assess whether factors other than coronary artery narrowing affect the maximal ST/HR slope which is used as an index of myocardial ischaemia. The slope was compared with indices of myocardial scarring or cardiac enlargement derived from x-ray and echocardiographic and angiographic investigations. In 35 (67%) patients the slope failed to predict the severity of myocardial ischaemia attributable to coronary artery narrowing; in 14 (27%) patients the slope overestimated the findings of coronary angiography and in 21 (40%) patients the slope underestimated the findings of coronary angiography. In the remaining 17 (33%) patients the slope accorded with the assessment of myocardial ischaemia by coronary angiography. Underestimation by the slope was associated with significantly poorer left ventricular function and a lower ejection fraction, indicating a greater degree of myocardial scarring.

To assess whether overestimation was related to cardiac enlargement with better preservation of ventricular function a follow up examination was performed six months after infarction. In the overestimated group 11 patients were followed up and seven of them showed a reduction in the maximal ST/HR slope which correlated with a reduction in the cardiothoracic ratio. This suggested that cardiac enlargement had contributed to myocardial ischaemia.

The results suggest that if the maximal ST/HR slope is an index of exercise induced myocardial ischaemia after recent infarction, it is subject to the influences of coronary artery narrowing as well as those of scarring and cardiac enlargement.

Studies in Leeds have shown that the maximal ST/HR slope is an index of myocardial ischaemia when related to coronary artery narrowing in selected populations of patients with angina,1 2 and that the slope is influenced by cardiac enlargement—for example in a selected population of patients with aortic valve disease and normal coronary arteriograms.3

In patients who have had an acute myocardial infarction exercise induced myocardial ischaemia has been related to coronary artery stenosis, though other factors, such as cardiac enlargement or the extent of myocardial scarring and muscle tissue loss, could be argued to affect the ischaemic process.4–6

We report a comparison of the maximal ST/HR slope and the results of angiography in patients with recent myocardial infarction as a further test of the reliability of the slope as an index of myocardial ischaemia.

Patients and methods

Consecutive patients were prospectively studied 4–6 weeks after myocardial infarction. The diagnosis of myocardial infarction was confirmed by the presence of at least two of the following criteria (a) typical history of chest pain lasting at least 30 minutes; (b) characteristic serial electrocardiographic changes, that is ST segment elevation, T wave inversion, and

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the appearance of new Q waves; (c) a rise in serum creatine kinase to at least twice the upper limit of normal. Patients with complications after infarction—for example cardiogenic shock, cardiac failure, arrhythmias, or conduction disturbances occurring 72 hours after infarction; acute haemodynamic complications—for example mitral regurgitation, pulmonary embolism; and unstable angina were not considered for study. Patients with uncontrolled hypertension, concomitant valve or chronic cardiac disease, or other medical conditions making exercise difficult were excluded from study. No patient on digoxin was included in the study.

All patients gave informed consent to the investigations and the study was approved by the local ethics committee.

We examined the effects of myocardial scarring and cardiac enlargement on myocardial ischaemia early after infarction as assessed by the maximal ST/HR slope. Wall scarrring was assessed by angiographic patterns of left ventricular wall motion and ejection fractions. To assess the influence of cardiac enlargement patients were re-examined six months after infarction and individual changes in heart size were measured, with the patients acting as their own controls. Changes in cardiothoracic ratio were measured on standard chest x-rays and ventricular dimensions were obtained by cross sectional echocardiography. A blind comparison was made between the maximal ST/HR slope and the results of angiocardiography, chest x-rays, and echocardiography.

EXERCISE TEST

In each patient the exercise test was performed 4–6 weeks after a confirmed myocardial infarction. The details of the exercise test have been reported elsewhere. Briefly, the exercise test was performed on an electrically braked bicycle ergometer with the patient in the upright position. Each test was preceded by a short preliminary exercise to determine the stepped increases in workload necessary to obtain stepped increases in heart rate of approximately 10 beats/minute, to enable adequate recordings by electrode replacement if required, and to familiarise the patient with the procedure. During the test the workload was increased every three minutes, with the test being terminated for the following reasons: anginal pain, ST segment depression > 0-3 mV, more than six multifocal ectopic impulses per minute or tachycardia, a decrease in blood pressure, or exhaustion.

The electrocardiogram was recorded from 13 leads—12 conventional leads and a bipolar lead (CM5)—with an ink jet Mingograph recorder (Siemens type 62). The leads were calibrated by setting the amplifier gain so that a 1 mV signal caused a displacement of 10 mm. Records from the 13 electrocardiographic leads were obtained at rest, during the last minute of each exercise step, and for at least five minutes after the end of exercise. The electrocardiogram was monitored throughout the test and recovery period. Systemic blood pressure was measured before, during, the third minute of each exercise step, and during the recovery period.

The ST segment level was measured at a point 80 ms after the end of the QRS complex; a line drawn between consecutive PR segments was taken as the zero reference. This measurement was made with a magnifying glass fitted with a graticule marked in 0-1 mm divisions. The heart rate (beats/minute) was calculated by measuring the R–R interval on the electrocardiogram.

The measurements of ST segment level and heart rate were made from electrocardiographic records obtained during the steady state (heart rate value within ±5% of the mean) attained during the third minute of each exercise step. The values of heart rate and ST segment level were taken as the average value measured in at least 10 consecutive cardiac cycles obtained from records of all 13 electrocardiographic leads.

The maximal ST/HR slope was derived by performing regression analysis on the relation between the ST segment level and heart rate in each of the 13 electrocardiographic leads. In each lead the steepest slope of the computed regression lines which showed a linear regression was noted. The maximal ST/HR slope of all the 13 electrocardiographic leads was used as an index of myocardial ischaemia and this has units of mm per beat minute per 1000. 

ANGIOCARDIOGRAPHY

In each patient within one week of the exercise test selective coronary arteriography and left ventriculography were performed and reported on by the cardiologists without knowledge of the results of the exercise test.

Significant coronary artery disease was defined as luminal narrowing of the diameter of > 75% in any of the three major coronary arteries. We used the same method of scoring angiograms so that we could compare the results of our study with previous studies in patients with angina. Percentage narrowing was assessed by a visual impression based on views of the vessels in more than one plane. The degree of stenosis of a long lesion was estimated at its narrowest point and in vessels that contained more than one lesion the degree of stenosis was that of the most severe lesion. Patients were divided into four groups: those with no significant coronary artery disease and those with single, double, and triple ves-
Significant narrowing of the left main coronary artery was considered to be equivalent to significant narrowing of its two major branches and hence was labelled double vessel disease.

Assessment of the left ventricular function from ventriculography was made by visual impression. The left ventricular angiogram was scored on a scale of 0 to 4. The score was intended as an index of the degree of scarring and thus took account of the mobility and dilatation of the left ventricle—a score of 0 being equivalent to normal left ventricular function and a score of 1 indicating mild impairment of left ventricular function with a range up to a score of 4 for severe impairment of left ventricular function.

Ejection fractions and end systolic and end diastolic areas and volumes were subsequently obtained from digitised tracings taken from the end systolic and end diastolic frames from the left ventricular angiogram. These volumes were derived from single plane left ventricular angiography in the right anterior oblique view at 30° to the vertical.

To compare the ventricular areas and volumes of the patients studied we used the diameter of the cardiac catheter as a scale and adjusted measurements accordingly. Ejection fraction was calculated from:

\[
\text{Ejection fraction} = \frac{\text{End diastolic volume} - \text{End systolic volume}}{\text{End diastolic volume}}
\]

Volume measurements from single plane angiography may not be precise in patients with myocardial infarction. In this study these measurements were intended as a further index of scarring for group comparison.

Assessment of Changes in Cardiac Size
Cardiothoracic ratio
All patients had a posteroanterior chest x-ray taken in the erect position and in deep inspiration within a week of the exercise test soon after infarction and on the same day as their follow-up exercise test. The cardiothoracic ratio was obtained in the usual way by dividing the transverse diameter of the heart by the internal diameter of the chest. Echocardiography
Left ventricular size was assessed by cross sectional echocardiography (Ultrasoundmer, Hewolyn). From the video recording of the echocardiographic examination the cross sectional areas of the left ventricle at end diastole in both the short axis view at the level of the papillary muscles and in the long axis apical four chamber view were measured, as was the long axis of the left ventricle.

Statistical analysis
Student’s unpaired t test, correlation, and \( \chi^2 \) testing were used as appropriate.

Results
Clinical Details
Fifty three consecutive patients prospectively underwent exercise testing 24-44 (mean 34.7) days after a confirmed myocardial infarction. One of these patients was excluded from the study because we could not obtain an electrocardiogram that was adequate for the derivation of the maximal ST/HR slope. Blind comparison of the value of the maximal ST/HR slope and the findings of angiography was made in 52 patients (six women, 46 men; aged 37-64 (52-6) years).

Twenty eight patients suffered an inferior myocardial infarction and in the remaining 24 patients there was an anterior infarction. Eight patients gave a history of previous myocardial infarction. At the time of examination the following drugs were being taken: \( \beta \) blocker (18 patients), thiazide diuretic (13 patients), frusemide (2 patients), nitrates (6 patients), nifedipine (2 patients), and methyldopa (1 patient). Twenty patients were receiving no drug treatment. In most patients followed up at six months there had been no change in drug treatment. Three patients were on additional vasodilator treatment (nifedipine or nitrates) which may increase the slope.
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Fig 2 Individual discrepancies between the assessment of myocardial ischaemia by the maximal ST/HR slope and by coronary angiography (in terms of the number of vessels difference) (mm per beat min per 1000) related to left ventricular score.

For instance if the slope suggested single vessel disease and angiography showed double vessel disease, this group would give a difference of +1. If angiography demonstrated single vessel disease and the slope value suggested double vessel disease, this would give a difference of −1. Where the slope gave intermediate values, say between single vessel and double vessel disease, this is taken as 1·5 for the purpose of comparison with angiography.

Comparison between the value of the maximal ST/HR slope and the angiographic extent of coronary artery narrowing

The maximal ST/HR slope increased as the severity of ischaemia worsened (fig 1). Eight patients had values of the slope in the previously described discrete categories for no significant disease, single, double, and triple vessel disease. There was agreement between coronary angiographic assessment of the severity of myocardial ischaemia and the slope in only 17 (33%) of the 52 patients. In the remaining 35 (67%) patients the slope failed to predict the severity of myocardial ischaemia; the slope either underestimated the angiographic extent of significant coronary artery narrowing (21 patients (40%)) or it overestimated the angiographic extent of coronary artery narrowing (14 patients (27%)). No patient with significant narrowing of all three coronary arteries had a maximal ST/HR slope equivalent to triple vessel disease.

Because the underestimation of the extent of coronary artery disease could be due to the effect of myocardial scarring, we examined indices of left ventricular function (the left ventricular score and ejection fraction).

Left ventricular function

Left ventricular score

For patients given a left ventricular score of 4, indicating severe left ventricular dilatation and severe impairment of wall mobility, the value of the slope consistently underestimated the extent of coronary artery narrowing (fig 2). While for those patients judged to have the best preserved left ventricular function—that is with a left ventricular score of 1—the slope consistently overestimated the extent of coronary artery narrowing (fig 2). There is a tendency for a discrepancy between the slope and angiography to be more likely if the left ventricular score is high; linear regression analysis showed that this trend is significant ($r = -0·68, p < 0·001$) (fig 2).

A higher left ventricular score is significantly associated with larger end systolic and larger end diastolic volumes, and a lower ejection fraction (fig 3).

Left ventricular volumes

Underestimation by the maximal ST/HR slope of the severity of coronary artery narrowing is associated with larger end systolic and end diastolic volumes (table). Similar results were obtained when we used left ventricular areas derived from single plane angiography.

Ejection fraction

Underestimation by the maximal ST/HR slope is associated with a lower ejection fraction (fig 4; $r = 0·60, p < 0·001$).

In patients with single vessel disease there is a significant tendency between the value of the maximal ST/HR slope and the left ventricular score ($r = -0·63, p < 0·05$), lower values of the slope being associated with higher scores (fig 5). A trend is seen when the value of the slope is related to the ejection fraction ($r = +0·57, p < 0·05$).

Follow up study

Of the total of 52 patients, 44 were re-examined six months after infarction; three had died, one had an embolic stroke, one had undergone coronary artery surgery, one had required permanent pacing for sinusatrial disease, and two patients declined further exercise tests.

All three patients who died had poor left ventricu-
lateral function (left ventricular scores of 3, 4, and 4; ejection fractions of 53, 27, and 29% respectively) and in all three the slope underestimated the severity of coronary artery narrowing.

To assess the influence of cardiac enlargement early after myocardial infarction we re-examined patients at six months and examined individual changes in heart size in relation to individual changes in the severity of myocardial ischaemia as assessed by the maximal ST/HR slope. In the 44 patients re-examined at six months there was a statistically significant reduction in cardiothoracic ratio (p < 0.02) from an initial mean (SD) value of 48.5 (4.5)%. The reductions in heart size as assessed by the cardiothoracic ratio were greater in the overestimate group, though this difference from the agreement and underestimate groups is not statistically significant.

Table  Ejection fraction and left ventricular volumes (mean (SD) (range)) for the three groups of patients in whom the maximal ST/HR slope showed either overestimation or underestimation or agreement with the findings of coronary angiography

<table>
<thead>
<tr>
<th></th>
<th>Overestimation (n = 14)</th>
<th>Agreement (n = 17)</th>
<th>Underestimation (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>64.8 (12.6) (36–89)</td>
<td>54.4 (9.3)* (33–67)</td>
<td>43.7 (10.5)* (22–64)</td>
</tr>
<tr>
<td>End diastolic volume (ml)</td>
<td>107.4 (28.2) (72–146)</td>
<td>107.5 (29) (75–165)</td>
<td>141.7 (44.4)§ (79–230)</td>
</tr>
<tr>
<td>End systolic volume (ml)</td>
<td>39.1 (17.0) (10–68)</td>
<td>49.5 (20.2) (33–111)</td>
<td>81.7 (34.8)§ (32–180)</td>
</tr>
</tbody>
</table>

*Overestimate vs agreement, p < 0.02.
†Overestimate vs underestimate, p < 0.001.
‡Agreement vs underestimate, p < 0.01.
§Agreement or overestimate vs underestimate, p < 0.02.
correlation between a reduction in cardiothoracic ratio and the maximal ST/HR slope over a period of six months was found only in one of the 18 patients from the underestimate group who were re-examined ($\chi^2$, p < 0.01).

Of the 17 patients examined by echocardiography we had adequate images for measurement of left ventricular areas at end diastole in eight. The change in cardiothoracic ratio for these eight patients correlated with the change in the cross sectional end diastolic area of the left ventricle obtained from the apical four chamber view on cross sectional echocardiography ($r = 0.79$, p < 0.02).

**Discussion**

**MAXIMAL ST/HR SLOPE AS INDEX OF MYOCARDIAL ISCHAEMIA**

The maximal ST/HR slope has been proposed as an index of myocardial ischaemia. In trials of hospital patients presenting with angina in Leeds, it was shown that the slope was 96.5% successful in detecting significant coronary artery stenosis (as defined above). These patients were selected; they did not have left ventricular aneurysm, or conditions causing cardiac enlargement—for example valvular heart disease—and they were not examined within six months of myocardial infarction.

In a subsequent trial, patients with aortic valve disease and cardiac enlargement were examined. In the absence of coronary artery narrowing cardiac enlargement was associated with values of the maximal ST/HR slope equivalent to coronary heart disease. Left ventricular dilatation and hypertrophy is a reported cause of myocardial ischaemia.

Attempts to reproduce the accuracy found in Leeds have to date been unsuccessful, the reason for this is not known. It may be related to the characteristics of the patients studied, use of different techniques, and differences in angiographic interpretation. Other studies of the ST segment and heart rate relation that used different techniques and different angiographic criteria have suggested that this index provides a reliable assessment of the presence and severity of coronary disease in patients with angina. False positive results have been reported in patients with aortic regurgitation and false negative results in patients with previous myocardial infarction.

This evidence suggests that the ability of the maximal ST/HR slope to detect any one cardiac or coronary lesion that leads to myocardial ischaemia must depend on the characteristics of the selected population being studied. Patients early after myocardial infarction could have, in addition to any coronary narrowing, cardiac lesions, such as enlargement or

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**Fig 5** Individual values of the maximal ST/HR slope (mm per beat min per 1000) related to left ventricular score for the 25 patients with single vessel disease. The range of the slope for single vessel (I) disease as found in selected patients with angina is shown by the broken lines.

Eleven of the 14 patients in whom the slope had overestimated the extent of coronary artery narrowing were re-examined at six months. Eight of these 11 patients showed a reduction in heart size as assessed by the cardiothoracic ratio. Seven of these eight patients had an associated reduction in the maximal ST/HR slope (fig 6). In contrast, such a

**Fig 6** Individual changes in cardiothoracic ratio and maximal ST/HR slope (mm per beat min per 1000) for seven patients from the group in which the slope overestimated the findings of coronary angiography. The ranges of the maximal ST/HR slope equivalent to single vessel (I), double vessel (II), or triple vessel disease (III), as obtained in selected patients with angina, are given on the right of the figure.
scarring, that influence myocardial ischaemia. For instance, left ventricular wall scarring and loss of myocardium may limit myocardial ischaemia whereas cardiac enlargement with a better preserved myocardium may predispose to myocardial ischaemia.\(^4\)\(^-\)\(^6\) The present trial was planned to examine the effects of these factors on the maximal ST/HR slope, which is used as an index of myocardial ischaemia. We used the same techniques in assessing the maximal ST/HR slope that were used in previous studies\(^11\)\(^\)\(^12\) so that we could compare the results of the present trial with those of earlier ones.

**FINDINGS OF THE PRESENT STUDY**

The present findings suggest that coronary artery narrowing, myocardial scarring, and cardiac enlargement may affect the maximal ST/HR slope after recent myocardial infarction. Myocardial scarring would be associated with left ventricular dilatation, accompanied by an increase in end systolic volume, and reduced wall mobility. The left ventricular score was used as an index of scarring; the finding of an association between high scores and larger left ventricular volumes and a lower ejection fraction (fig 3) confirms that the score was an adequate, though crude, index of scarring. Underestimation of the findings of coronary angiography by the maximal ST/HR slope was found to be significantly associated with the index of myocardial scarring; namely, higher left ventricular scores (fig 2), and also with larger left ventricular volumes and a lower ejection fraction (table 1 and fig 4).

It could be argued that two “opposing” areas of myocardial ischaemia could be cancelling out their electrocardiographic manifestations, though there is no evidence for such an effect from experience with the maximal ST/HR slope in patients with angina.\(^1\)

The ST segment elevation associated with aneurysm formation could also be said to mask the presence of ischaemia, though aneurysms may be regarded as mainly representing scar tissue and would be included in the index of scarring used. In the present study many of the patients who had a maximal ST/HR slope of zero had significant narrowing of only the infarct related coronary artery, and this was often associated with poor left ventricular function and in some with aneurysm formation.

One of the principal determinants of prognosis in patients after myocardial infarction is the extent of myocardial damage—a larger infarct being associated with a poorer prognosis.\(^4\)\(^\)\(^4\) Though the number of patients in the present study is too small for adequate statistical analysis, the patients in whom the slope underestimated the angiographic extent of coronary artery narrowing had the highest mortality—all three patients who died came from this group. All these findings suggest that scarring may limit myocardial ischaemia as assessed by a functional index, the maximal ST/HR slope.

In this study larger left ventricular volumes were associated with indices of a greater degree of myocardial scarring. The above findings also suggest that scarring may limit myocardial ischaemia. In patients with well preserved left ventricular function—that is less scarring—it may be possible to demonstrate the effect of cardiac enlargement on myocardial ischaemia.

The influence of cardiac enlargement was assessed by correlating individual changes in heart size in the six months after myocardial infarction with changes in the maximal ST/HR slope. The cardiothoracic ratio is an accepted measure of change in heart size in an individual,\(^9\) though it is not accurate for comparisons between patients. In this study correlation with echocardiographic measurements showed that changes in cardiothoracic ratio reflected alterations in left ventricular dimensions. Examination of these indices showed that there was evidence that ventricular size affected the maximal ST/HR slope.

In the group in which the slope overestimated left ventricular damage (that is those with the best preserved left ventricular function) most patients demonstrated a reduction in cardiothoracic ratio which was associated with a reduction in the maximal ST/HR slope. The reduction in the slope exceeded the 95% tolerance limits of obtaining the slope,\(^1\) and for some patients involved a shift from the range of double vessel disease to single vessel disease.

In this study we obtained values of the slope that were intermediate between the categories of single and double vessel disease and double and triple vessel disease. It is our experience that such values are often obtained when cardiac enlargement has been evident.\(^3\)

Even in the face of factors such as scarring and cardiac enlargement that influence myocardial ischaemia there was still a tendency for the assessment of myocardial ischaemia by the maximal ST/HR slope to agree with assessment by coronary angiography (fig 1). Where the slope agreed with the angiographic findings coronary artery narrowing may not have been the principal influence on myocardial ischaemia since scarring and cardiac enlargement could also have been influencing the results.

**IMPLICATIONS**

The above findings suggest that, in addition to being dependent on the severity of coronary artery disease, myocardial ischaemia early after myocardial infarction may be limited by scarring and may be increased by cardiac enlargement. This implies that in individual patients exercise induced myocardial
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ischaemia after recent myocardial infarction is determined by at least these three factors; however, the relative contribution of each is not known.

Cardiac enlargement in patients with myocardial infarction is also related to the degree of scarring, and so differs from the enlargement seen with aortic valve disease. The present findings suggest that scarring may limit myocardial ischaemia attributable to coronary artery narrowing, and scarring also is likely to limit the influence of cardiac enlargement on the ischaemic process. This is evident from the group in which the slope underestimated the extent of coronary artery narrowing and who also had the largest left ventricular volumes (table). Animal studies have shown that a relative increase in left ventricular volume occurs even with small infarctions. Where the effect of scarring is not great it should be possible to detect, using an index of myocardial ischaemia, the contribution of cardiac enlargement to the ischaemic process. This is supported by the findings from the patients in whom the slope overestimated the severity of coronary artery narrowing; this group had the best preserved left ventricular function.

Other possible explanations for the overestimation of coronary artery narrowing by the slope that was seen in some patients include drug treatment, distal coronary artery disease, and haematological abnormalities. An increase in the maximal ST/HR slope was seen when vasodilating drugs were used in patients with stable angina, however, only two of the patients in the overestimate group were on such treatment. It is possible that distal coronary disease may be contributing to this “extra ischaemia”: trials of the use of the maximal ST/HR slope in patients with stable angina did not assess this aspect. Abnormalities of platelet morphology have been reported in patients after acute myocardial infarction, though further study is required to find out whether these changes contribute to ischaemia in the weeks after myocardial infarction.

The present findings may help to explain the reported discrepancy in the published reports regarding the value of exercise electrocardiography after infarction in detecting “multivessel disease”. Although the index of myocardial ischaemia used in such trials is open to criticism, the discrepancy in results may also be due to influences other than coronary artery disease on myocardial ischaemia.

CONCLUSION

This study involving blind comparison of the maximal ST/HR slope with angiocardiology was aimed at testing the accuracy of the slope as an index of myocardial ischaemia early after myocardial infarction. The slope has been shown to be sensitive to the modifying influences of myocardial scarring and cardiac enlargement upon myocardial ischaemia soon after infarction. Exercise induced ischaemia early after myocardial infarction is influenced by myocardial scarring, cardiac enlargement, and significant narrowing of the coronary artery. Because ischaemia early after myocardial infarction is multifactorial, unlike ischaemia in patients with stable angina, the slope cannot be expected to detect the extent of significant coronary artery narrowing.

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