Early exercise testing after treatment with thrombolytic drugs for acute myocardial infarction: importance of reciprocal ST segment depression

Robert N Stevenson, Velaitham Umachandran, Kulasegaram Ranjadayalan, Robin H Roberts, Adam D Timmis

Abstract

Objective—To investigate the clinical importance of reciprocal ST depression induced by exercise testing early after acute myocardial infarction in patients treated with thrombolysis.

Design—Prospective observational study.

Setting—District general hospital in London.

Subjects—202 patients (170 men) aged 33–69 with acute myocardial infarction treated with thrombolysis.

Main outcome measures—All patients underwent exercise testing and coronary arteriography. ST depression induced by exercise was classified as either reciprocal (associated with ST elevation) or isolated (occurring on its own). The relation between reciprocal ST depression and the following end points was studied: characteristics of the infarct, left ventricular ejection fraction, extent of coronary artery disease on arteriography, and presence of angina induced by exercise.

Results—Reciprocal ST depression occurred almost exclusively in Q wave infarctions and was associated with a lower overall ejection fraction than isolated ST depression. It tended to be associated with persistent occlusion of the coronary artery related to the infarct and did not indicate remote ischaemia due to multivessel coronary disease. Unlike isolated ST depression, reciprocal ST depression was not associated with angina induced by exercise.

Conclusions—Reciprocal ST depression induced by exercise is usually associated with extensive Q wave infarctions and persistent occlusion of the artery related to the infarct. It does not seem to indicate reversible ischaemia and should not be used as a non-invasive marker of multivessel disease in the assessment of requirements for further investigation soon after acute myocardial infarction.

Introduction

In acute myocardial infarction ST segment elevation in the electrocardiogram obtained on presentation is often accompanied by reciprocal ST depression (changes in leads related to opposing areas of the heart). Debate on the importance of this reciprocal ST depression continues, with opinion divided on whether it represents remote ischaemia due to multivessel coronary disease¹ or a passive electrical phenomenon.^{2–4} Similarly, on treadmill exercise testing after infarction ST elevation in the leads related to the infarct is often accompanied by reciprocal ST depression in the leads related to the opposing areas.⁵ Whereas much is known about reciprocal ST change in the presenting electrocardiogram, little information

exists on its importance during exercise testing; whether it represents inducible myocardial ischaemia (in opposing areas) or a passive electrical phenomenon remains unclear. The distinction is important because exercise testing after infarction is widely used on the premise that ST depression indicates residual reversible ischaemia, which may in turn suggest severe coronary disease.

To clarify whether reciprocal ST depression induced by exercise indicates reversible myocardial ischaemia, we have studied how it relates to the presence of coronary artery disease in a group of patients undergoing early exercise testing and coronary arteriography after treatment with thrombolytic drugs.

Methods

PATIENT SELECTION

The study group was selected from 256 consecutive patients who presented to a general hospital in east London and received intravenous thrombolytic drug treatment for acute myocardial infarction. Acute myocardial infarction was diagnosed on the basis of any two of the following three criteria: typical chest pain, ST elevation of ≥ 0.1 mV in at least one standard or two precordial leads, and a rise in serum creatine kinase concentration to > 400 IU/l. Most of the patients were treated with streptokinase 1.5 million IU infused over one hour, but, because we were participating in the multicentre third international study of infarct survival during part of the recruitment period, 40 patients were randomised to receive streptokinase (1.5 million IU infused over one hour), alteplase (100 mg infused over four hours), or anistreplase (30 IU injected over three minutes). The specific criteria for inclusion were acute myocardial infarction as defined above; treatment with a thrombolytic agent; no complications as an inpatient and no continuing chest pain, electrical instability, or heart failure; the ability to perform an exercise test that was stopped when symptoms appeared; and the absence of abnormalities that might prevent interpretation of the exercise electrocardiogram, such as left bundle branch block, paced rhythms, and ST-T changes induced by digoxin.

At the time of this study coronary arteriography was routinely offered to all patients following acute infarction under the age of 70. The study group comprised the 202 patients who underwent coronary arteriography as a result of this clinical policy. The patients who did not undergo arteriography were aged over 70 (31) or refused to give consent (15); the reason for the remaining eight patients not undergoing arteriography was not recorded.

The study was approved by the local ethics committee, and all patients gave written informed consent.

Department of Cardiology,
London Chest Hospital,
London E2 9JX
Robert N Stevenson,
research registrar
Robin H Roberts, research
registrar
Adam D Timmis, consultant
cardiologist

Department of Cardiology,
Newham General Hospital,
London E13 8SL
Velaitham Umachandran,
research registrar
Kulasegaram Ranjadayalan,
staff physician

Correspondence to:
Dr Robert N Stevenson,
Huddersfield Royal
Infirmary, Huddersfield
HD3 3EA.

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EXERCISE TESTING AND DRUG TREATMENT

Exercise testing with a modified version of the Bruce protocol was performed before or soon after discharge from hospital, a mean of 10 (range 7-21) days after infarction. Patients exercised for several periods of three minutes, with progressively increasing workloads. A 12 lead electrocardiogram was recorded before exercise, at the end of each stage, and at peak exercise. ST depression during the exercise test was regarded as important if it was horizontal or downsloping and ≥ 0.1 mV below the resting level when measured 0.08 s after the junction between the end of the QRS complex and the beginning of the ST segment (J point). ST elevation was regarded as important if it was >0.1 mV above the resting level when measured at the J point. ST depression induced by exercise was considered to be reciprocal if accompanied by ST elevation in leads related to another area of the heart—invariably the leads related to the infarct (fig 1)—and to be isolated if occurring on its own (fig 2).

All patients were prescribed aspirin 75-150 mg daily and other drug treatment for their heart disease as indicated. In the patients taking β blockers, treatment was not withdrawn as the diagnostic value of exercise testing is not greatly influenced by these drugs.⁶⁻⁸

CARDIAC CATHETERISATION

Patients underwent coronary arteriography and single plane (right anterior oblique) left ventriculography within 2-4 weeks of discharge from hospital. Multiple projections of the coronary arteries were recorded on cine film and reviewed by two experienced

TABLE 1—Relation of reciprocal and isolated ST depression to haemodynamic variables on exercise in 104 patients with ST depression induced by exercise. Values are means (95% confidence intervals)

Variable	ST depression		P value*
	Reciprocal (n=56)	Isolated (n=48)	
Exercise time (min)	8.98 (8.12 to 9.83)	8.51 (7.62 to 9.40)	0.45
Exercise load (metabolic equivalents)	7.21 (6.44 to 7.99)	6.83 (6.04 to 7.63)	0.49
Rise in blood pressure (mm Hg)	26.3 (21.0 to 31.6)	31.7 (24.9 to 38.6)	0.21
Rise in heart rate (beats/min)	54.4 (48.3 to 60.5)	56.9 (52.7 to 61.1)	0.40

*Means were compared with Student's *t* test.

observers, who were blind to the results of the exercise tests. Stenosis was defined as important if $>50\%$ luminal narrowing (assessed by visual inspection) occurred in any of the three major coronary vessels or their large branches. Patients were considered to have multivessel disease if important stenoses occurred in two or three vessels, excluding the right coronary artery when this was non-dominant. The coronary artery related to the infarct was assessed on the basis of the criteria used in the thrombolysis in myocardial infarction trial,⁹ with patency being defined as grade 2 or 3. The left ventricular ejection fraction was measured according to the method of Sandler and Dodge.¹⁰

STATISTICAL ANALYSIS

All data were expressed as means with standard deviations or 95% confidence intervals. Continuous variables were compared with Student's *t* test after a normal distribution had been established. The distributions of discrete variables among groups were compared by the χ^2 test. A P value of <0.05 was considered to be significant. Sensitivity was regarded as the proportion of patients with the arteriographic end point who were correctly identified by the exercise test and specificity as the proportion of patients without the arteriographic end point who were correctly identified by the test. Positive predictive accuracy was regarded as the proportion of patients with a positive response who had the arteriographic end point and negative predictive accuracy as the proportion of patients with a negative result who did not have the arteriographic end point.

Results

The study group comprised 202 patients (170 men; mean age 56 (range 33-69)) with acute myocardial infarction treated by thrombolysis, all of whom underwent exercise testing after a mean of 10 (SD 9) days. Coronary arteriography was performed after 30 (16) days and showed grade 2 or 3 patency of the coronary artery related to the infarct in 140 cases. In 98 this was the only diseased vessel, but the rest had multivessel disease affecting two major vessels (64) or three major vessels (40).

ST depression induced by exercise occurred in 104 of the 202 patients in the study. In 48 it was found to be isolated, but in the rest it was found to be reciprocal and associated with ST elevation in the leads related to the infarct. There were no significant differences between patients with isolated and reciprocal ST depression with regard to exercise tolerance or haemodynamic responses (table I).

The presence of ST depression induced by exercise, whether or not it was reciprocal, did not differ significantly between anterior and inferior infarction (table II). While reciprocal ST depression occurred almost exclusively in Q wave infarctions, however, non-Q wave infarctions occurred in a higher pro-

FIG 1—Electrocardiogram during peak exercise showing ST elevation in anterior leads related to infarct associated with reciprocal ST depression in inferior leads

FIG 2—Electrocardiogram during peak exercise showing isolated ST depression in anterior leads

TABLE II—Relation of ST depression induced by exercise to presence of Q wave infarction, location of infarct, patency of coronary artery related to infarct, extent of coronary disease, and angina induced by exercise. Values are numbers (percentages) of patients

	ST depression			χ^2 (2 df)	P value
	Absent (n=98)	Reciprocal (n=56)	Isolated (n=48)		
Q wave infarct (n=162)	80 (82)	53 (95)	29 (60)	19.31	<0.001
Anterior infarct site (n=105)	51 (52)	32 (57)	22 (46)	1.32	0.5
Patent artery related to infarct (n=140)	79 (81)	30 (54)	31 (65)	12.91	<0.01
Multivessel disease (n=104)	43 (44)	27 (48)	34 (71)	9.70	0.002
Angina induced by exercise (n=41)	14 (14)	11 (20)	16 (33)	7.25	0.03

TABLE III—Diagnostic value (sensitivity, specificity, and positive and negative predictive accuracy) of ST variables for predicting multivessel coronary disease and patency of artery related to infarct. Values are percentages

	ST depression induced by exercise		
	Any	Reciprocal	Isolated
Patent artery related to infarct (n=140):			
Sensitivity	44	22	22
Specificity	31	58	75
Positive predictive accuracy	59	55	67
Negative predictive accuracy	20	25	30
Multivessel disease (n=104):			
Sensitivity	59	25	33
Specificity	56	70	86
Positive predictive accuracy	59	47	72
Negative predictive accuracy	56	47	54

portion of patients with isolated ST depression (19/48 (40%)) than in patients either without ST depression (18/98 (18%)) or with reciprocal ST depression (3/56 (5%)) ($P<0.001$).

Angina induced by exercise occurred as commonly in patients with reciprocal ST depression (11/56 (20%)) as in those without ST depression (14/98 (14%)) (table II). In contrast, it occurred in a higher proportion of patients with isolated ST depression (16/48 (33%)) than in patients either without ST depression (14/98 (14%)) or with reciprocal ST depression (11/56 (20%)) ($P=0.03$).

ST depression induced by exercise was of no diagnostic value for predicting the patency of the artery related to the infarct. Coronary occlusion occurred in a higher proportion of patients with isolated ST depression (17/48 (35%)) or reciprocal ST depression (26/56 (46%)) than in patients without ST depression (19/98 (19%)) ($P<0.01$) (table II). Nevertheless, the classification of reciprocal ST depression as a negative response improved the specificity (75%) and predictive accuracy (67%) of ST depression in diagnosing coronary patency, albeit with a reduction in sensitivity (22%) (table III).

ST depression induced by exercise was more common in multivessel disease (61/104 (59%)) than single vessel disease (62/140 (44%)) ($P<0.05$) (table III), but the difference was not large and was of limited diagnostic value. Importantly, multivessel disease occurred in a higher proportion of patients with isolated ST depression (34/48 (71%)) than in patients either without ST depression (43/98 (44%)) or with reciprocal ST depression (27/56 (48%)) ($P=0.002$) (table II). Because reciprocal ST depression was not associated with multivessel disease the classification of reciprocal ST depression as a negative response therefore improved the specificity (86%) and predictive accuracy (72%) of ST depression for the diagnosis of multivessel disease, albeit with a reduction in sensitivity (33%).

The mean overall ejection fraction was lower in patients with reciprocal ST depression induced by exercise (54.1 (95% confidence interval 50.3 to 58.0)) than in patients either with isolated ST depression (60.0 (95% confidence interval 55.7 to 64.3); $P<0.04$)

or without ST depression (60.2 (95% confidence interval 56.7 to 63.7); $P=0.02$).

Discussion

RECIPROCAL ST DEPRESSION AND MULTIVESSEL DISEASE

Although reciprocal ST depression during exercise testing after infarction is common, accounting for nearly half of the episodes of ST depression in the present study, it has received little attention from previous investigators. Only two small arteriographic studies have analysed the relation of ST depression during exercise testing after infarction to multivessel disease, and these studies produced conflicting results.^{11,12} Our findings, in larger numbers of patients, concur with those of Walters *et al*¹¹ and show that reciprocal (in contrast to isolated) ST depression is not associated with multivessel disease. This distinction is important because exercise testing after infarction is widely used to select patients for coronary arteriography on the premise that ST depression induced by exercise is a sign of reversible myocardial ischaemia, which in turn may indicate extensive coronary disease and the need for revascularisation.

The confounding effects of reciprocal change in patients with a recent infarction may partially explain why the association between ST depression induced by exercise and multivessel disease has been so variable in previous studies, with values of 40–90% for sensitivity and 29–90% for specificity.^{13–18} Nevertheless, reasons for this variability are probably multifactorial, reflecting not only the prevalence and interpretation of reciprocal change but also differences in the patients selected and in the criteria adopted for a positive response. Sensitivity in particular is highly dependent on the patients selected and is spuriously increased by work up bias¹⁹; we avoided this problem by selecting all patients for arteriography, regardless of the results of the exercise test.

Debate on the mechanism of reciprocal ST depression continues, but, because in this study reciprocal ST depression occurred in leads related to opposing areas of the heart and was not associated with multivessel disease, an ischaemic aetiology is unlikely. Furthermore, the absence of a relation between reciprocal ST depression and angina induced by exercise suggests that it is a passive electrical phenomenon rather than a sign of reversible ischaemia. The argument for this mechanism is supported by studies of controlled coronary occlusion during angioplasty, in which reciprocal change is no more common in patients with multivessel disease than in those with single vessel disease²⁰ and is not associated with abnormality of the motion of the regional left ventricular wall in an opposing area.²¹

RECIPROCAL ST DEPRESSION AND CORONARY PATENCY

The finding that reciprocal change occurred almost exclusively in patients with severe Q wave infarction was not unexpected, given the established association between ST elevation induced by exercise in the leads related to the infarct and extensive myocardial injury.^{22–25} Presumably this association also accounts for the relation between reciprocal ST change and whether or not the artery related to the infarct has recanalised, persistent occlusion merely reflecting the deleterious effect of unsuccessful thrombolysis on the size of the infarct. This relation was much too weak, however, to be of clinical value in evaluating coronary patency. Moreover, because of the time that elapsed between exercise testing and cardiac catheterisation, relations between electrocardiographic changes induced by exercise and whether or not the artery related to the infarct had recanalised must be interpreted cautiously.

Clinical implications

- Treadmill exercise testing is widely used to select patients for coronary angiography after myocardial infarction
- Little information is available on the importance of reciprocal ST depression during exercise testing after infarction
- In this study reciprocal ST depression occurred almost exclusively in Q wave infarctions and was associated with a lower ejection fraction than isolated ST depression
- Reciprocal ST depression tended to be associated with an occluded coronary artery related to the infarct and was not associated with multivessel coronary disease
- Reciprocal ST depression occurring during exercise testing after infarction does not seem to indicate reversible ischaemia

LIMITATIONS OF THE STUDY

The potential limitations of the study relate to the interpretation of coronary arteriograms and exercise electrocardiograms. Luminal narrowing of >50%, therefore, was chosen to define an important coronary stenosis as this degree of narrowing could be easily judged by visual inspection of the coronary arteriograms. The results might have been different had a cut off value of 70% luminal narrowing been selected, although this would probably not have resulted in a large number of patients being reclassified in terms of single versus multivessel disease. The measurement of ST changes in exercise electrocardiograms may be difficult when pathological Q waves are present, particularly at high heart rates as the ST segment tends to merge with the T wave. In practice, however, this was rarely a problem, and any errors in measurement that did occur would have been random rather than systematic and probably did not substantially influence the results of the study. It should also be emphasised that, although the study relates primarily to the interpretation of changes in the ST segment, other features of the exercise test, such as the blood pressure response and exercise time, are equally important in terms of the assessment of the risk after infarction.

CONCLUSIONS

This study showed that reciprocal ST depression was common in patients undergoing early exercise testing after acute myocardial infarction and was usually associated with extensive Q wave infarction and persistent occlusion of the artery related to the infarct. Importantly, reciprocal ST depression was not associated with multivessel disease. Because reciprocal ST depression induced by exercise does not share the arteriographic correlates of isolated ST depression it should not be used as a non-invasive marker of multivessel disease in the assessment of requirements

for further investigation early after acute myocardial infarction.

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A "PATIENT" THAT CHANGED OUR PRACTICE

An anaesthetised cockroach

He was anaesthetised unintentionally. I had reached the stage of closing the abdominal wall in the caesarean section and it was nearly midnight, when the sister, the nurse anaesthetist, said, "Doctor, when you have finished would you look at the bellows, because there is a cockroach in it. It was kicking but now it is either dead or anaesthetised."

Sure enough under the plastic cover of the outlet valve was an immobile cockroach and tipping the outlet port slightly downwards and vigorous pumping of the bellows caused it to fall out and crawl groggily across the floor of the theatre office. Sister (though a Franciscan) was going to step on him, but I threw him out of the window.

Had he been in the tubing, however, we might not have known he was there until he entered our patient's respiratory tree. We now tie a gauze swab over the face mask in position on our anaesthetic circuit and over the air intake when we finish operating. We think that this will keep out cockroaches, would be difficult to overlook when starting to use the machine next time, and will not be lethal if it is overlooked.

The theatre doors do not fit well enough to keep out cockroaches or lizards but provided they are closed they keep out our free range goats, pigs, and chickens.—ANNE SEYMOUR is a surgeon at the Catholic Hospital, Njinikom, Cameroon