Accurate detection of triple vessel disease in patients with exercise induced ST segment depression after infarction

D MANNERING, E D BENNETT, D E WARD, K DAWKINS, M DANCY, H VALANTINE, N MEHTA

From the Departments of Medicine One and Cardiology, St George's Hospital and Medical School, London

SUMMARY The severity of coronary artery disease is an important determinant of prognosis after acute myocardial infarction. The ability of a symptom limited exercise test to predict the presence of triple vessel disease was assessed in 221 patients three weeks after infarction. Coronary angiography was performed in patients with exercise induced ST segment depression. The presence of ST segment depression alone was poorly indicative of triple vessel disease; however, some specific features of ST segment changes on exercise were of predictive value. Downsloping ST segment configuration alone or horizontal ST segment depression associated with an early onset and a late recovery time after exercise correctly identified 30 (90%) of 33 patients with triple vessel disease whereas it incorrectly identified only 6 (15%) of 39 patients with single and double vessel disease. An abnormal blood pressure response was also predictive.

In patients with ST segment depression after infarction triple vessel disease can be detected accurately by a combination of the electrocardiographic and haemodynamic variables attained on exercise.

Exercise testing in patients early after myocardial infarction is a valuable diagnostic and prognostic technique. One year mortality in patients with exercise induced ST segment depression has been shown to be 25% compared with 2% in patients with no ST segment depression.¹ Even though the one year mortality rate is significantly higher in patients with ST segment depression on exercise, most of these patients are not at high risk of further cardiac events. There is thus a need to identify more accurately the "at risk" group of patients who may benefit from invasive diagnostic and therapeutic techniques. Furthermore, it has been suggested that reduced exercise tolerance or a poor haemodynamic response on exercise may be more predictive of later complications than ST segment changes.²

The purpose of this study was to quantify specific ST segment changes on exercise together with the haemodynamic responses on exercise in a group of

patients three weeks after a myocardial infarction and to relate these findings to their subsequent coronary anatomy.

Patients and methods

PATIENTS

The study group consisted of 221 consecutive patients under the age of 70 years in whom the diagnosis of a myocardial infarction was based on the presence of at least two of the following three criteria: (a) a typical history of chest pain persisting for at least 30 minutes, (b) new Q waves or evolution of ST-T wave changes, (c) a rise in the cardiac enzyme concentrations of aspartate transaminase, hydroxybutyrate dehydrogenase, or creatine kinase to at least twice the upper limit of normal. The average (SE) age was 57 (4); 40 (18%) were female. Ninety three (42.2%) had had an anterior infarction, 94 (42.6%) an inferior infarction, 20 (8.9%) a lateral infarction, 4 (2.0%) a true posterior infarction, and 10 (4.4%) had no infarction site indicated by the electrocardiogram. Four showed left bundle branch block and four right bundle branch block on the resting

Requests for reprints to Mr D Mannering, Department of Medicine 1, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

Accepted for publication 8 October 1986

Figure Characterisation of ST segment configuration at peak exercise.

electrocardiogram. One hundred and twenty three patients were taking β blockers at the time of exercise. Patients with valvar heart disease or aortic stenosis were excluded from the study.

EXERCISE TESTING

Symptom limited exercise testing was carried out on a motor driven treadmill by the Bruce protocol.³ Patients exercised for 3 min stages at progressively increasing work loads. A 12 lead electrocardiogram was recorded before exercise with the patient supine and upright, at the end of each 3 minute stage of exercise, immediately after exercise, and every minute during recovery. In addition, leads II, V2, and V5 were continuously monitored throughout exercise. Blood pressure was measured on the right arm by the standard cuff method at the same time as the electrocardiogram was recorded.

Exercise was continued until one of the following end points: (a) >3 mm ST segment depression 80 ms after the J point in any lead; (b) a fall in systolic blood pressure; (c) occurrence of chest pain, dyspnoea, fatigue, or dizziness; (d) leg cramps. A test was defined as positive if ≥ 1 mm ST segment depression was recorded in any lead. ST segment depression was categorised as slowly unsloping, horizontal, and downsloping configurations (figure). Total exercise time and time to onset of significant ST segment depression on exercise were recorded together with the recovery time from ST segment depression after exercise. The increase in systolic blood pressure at peak exercise was expressed as the

percentage increase from the resting value (systolic blood pressure increase). Patients in whom systolic blood pressure did not increase by $>10\%$ of the resting value at peak exercise were considered to have a poor exercise blood pressure response. The heart rate at the onset of significant ST depression was expressed as a percentage increase from the resting value (heart rate at onset).

CORONARY ANGIOGRAPHY

Coronary arteriography was performed at 2–4 weeks after the exercise test on patients with significant ST segment depression who agreed to undergo the procedure. Twelve patients with no ST segment depression underwent this procedure for clinical reasons. The arteriograms were viewed by a radiologist who was unaware of the exercise test findings. Significant coronary artery disease was defined as $>70\%$ proximal luminal narrowing in either the left anterior descending, circumflex, or right coronary arteries or the left main stem. Patients were then classified as having single, double, or triple vessel disease.

FOLLOW UP

Patients with a diagnosis of significant triple vessel or left main disease were referred for coronary artery bypass surgery together with those patients in whom symptoms persisted despite optimal medical treatment and in whom the coronary anatomy was suitable for surgery. All other patients were managed medically.

STATISTICAL ANALYSIS

Unpaired student *t* tests were applied where appropriate to test for significant differences in the measured exercise variables between the negative and positive test groups and between the patient groups with single, double, and triple vessel disease. We used discriminant analysis (*Statistical Package for the Social Sciences*) to distinguish statistically between patients with (a) single and double vessel disease and (b) triple vessel disease, using the exercise variables described above as discriminant variables. The optimal discriminatory points were used to determine the sensitivity and specificity of these exercise variables.

Results

Significant ST segment depression (positive test) was recorded in 89 (40%) patients, 72 of whom underwent coronary angiography. The remaining 17 patients with a positive test either refused to undergo this procedure or had more serious underlying medical conditions. Of the patients who underwent angiography, 24 were diagnosed as having single vessel disease, 15 double vessel disease, and 33 triple vessel disease. Of the 132 patients with no ST segment depression (negative test), 12 underwent coronary angiography for clinical reasons: three were <35 years of age, four had significant chest pain, one had a suspected left ventricular aneurysm, one had early exercise induced left bundle branch block, and three became hypotensive on exercise. Single vessel disease was diagnosed in nine, double vessel disease in three; none had triple vessel disease.

There was no significant difference in the resting heart rate between patients with a negative test and those with a positive test (77 beats/minute for both groups) or between the rates attained at peak exercise (127 beats/minute for both groups). Exercise time was significantly longer in patients with a negative test (6.7 (0.3) minutes) than in the positive test

group (5.7 (0.3) minutes) ($p < 0.01$). The mean (SE) systolic blood pressure increase in the negative test group was 26 (3)% compared with 16 (2)% in the positive test group ($p < 0.001$).

Table 1 shows the mean onset time, recovery time, and ST segment configuration together with the systolic blood pressure increase, heart rate increase at ST depression, and the exercise time for the single, double, and triple vessel disease groups together with the respective *p* values. Table 2 shows the sensitivity and specificity attained for each exercise variable in distinguishing the two groups: (a) single and double vessel disease and (b) triple vessel disease.

Discriminant analysis demonstrated that downsloping ST segment configuration was the most accurate single exercise variable in predicting severity of disease; it correctly classified 77.8% of patients. This was followed by ST segment recovery time (76.4%); the onset time to significant ST segment depression (75.0%); the increase in heart rate at onset of ST depression (72.2%), and the blood pressure response to exercise (70.8%). By combining all these exercise variables 90.3% of patients were correctly classified ($p < 0.01$).

None of the 12 patients with upsloping ST seg-

Table 2 Sensitivity and specificity of the exercise variables used to distinguish between single and double vessel disease and triple vessel disease

Exercise variable	Sensitivity (%)	Specificity (%)
Downsloping ST depression	94.9	57.6
Recovery time from ST depression (≥ 6 min)	82.1	69.7
Onset time to ST depression (≤ 3 min)	66.7	84.8
Increase in heart rate at ST depression ($< 40\%$)	59.0	87.9
Increase in systolic blood pressure ($\leq 10\%$)	69.2	72.7
Exercise time (min)	66.7	60.6

Table 1 Mean (SE) values of all exercise variables in relation to the severity of coronary disease

Exercise variable	Severity of disease			<i>p</i> values		
	Single	Double	Triple	Single vs double	Single vs triple	Double vs triple
Heart rate (rest) (beats/min)	75 (3)	76 (4)	80 (3)	NS	NS	NS
Heart rate (peak) (beats/min)	128 (4)	127 (6)	124 (4)	NS	NS	NS
Onset time to ST depression (min)	5.5 (0.4)	2.9 (0.4)	2.0 (0.2)	<0.001	<0.001	<0.05
Recovery time from ST depression (min)	3.9 (0.5)	5.3 (0.7)	8.3 (0.5)	NS	<0.001	<0.001
ST segment configuration (No):						
Upsloping	11	1	0			
Horizontal	13	12	14		$\chi^2 p < 0.001$	
Downsloping	0	2	19			
Systolic blood pressure increase (%)	24.4 (3.2)	15.8 (4.7)	5.1 (2.7)	NS	<0.001	<0.05
Increase in heart rate at onset of ST depression (%)	63.4 (5.4)	50.3 (8.8)	29.7 (3.4)	NS	<0.01	<0.001
Exercise time (min)	6.9 (0.5)	5.8 (0.6)	4.9 (0.4)	NS	<0.01	NS

Table 3 Association of early onset time to ST segment depression and late recovery time with severity of disease in patients with horizontal ST segment depression

Severity of disease	Group 1 Onset time > 3 min Recovery time < 6 min	Group 2 Onset time ≤ 3 min Recovery time < 6 min	Group 3 Onset time > 3 min Recovery time ≥ 6 min	Group 4 Onset time ≤ 3 min Recovery time ≥ 6 min
Single/double vessel	10	8	3	4
Triple vessel	1	1	1	11

ment depression had triple vessel disease whereas 19 of the 21 with downsloping ST segment depression had triple vessel disease. Of the 39 patients with horizontal ST segment depression, however, 14 had triple vessel disease. To separate further this group of patients with horizontal ST segment depression, we used the second and third most powerful discriminant variables (an onset time to significant ST segment depression of ≤ 3 minutes and a recovery time after exercise of ≥ 6 minutes) in association with horizontal ST segment configuration. Four groups of patients with horizontal ST segment depression were then defined:

Group 1—Patients with an onset time of > 3 minutes and a recovery time of < 6 minutes.

Group 2—Patients with an onset time of ≤ 3 minutes and a recovery time of < 6 minutes.

Group 3—Patients with an onset time of > 3 minutes and a recovery time of ≥ 6 minutes.

Group 4—Patients with onset time of ≤ 3 minutes and a recovery time of ≥ 6 minutes. Table 3 shows these results.

Seventy nine per cent of the 14 patients with triple vessel disease and horizontal ST segment depression were in group 4 whereas only 16% of those with single or double vessel disease with horizontal ST segment depression were in group 4.

β BLOCKERS

Fifty four (44%) of the 123 patients taking β blockers had significant ST segment depression on exercise compared with 39 (39%) of the 99 patients not taking β blockers. There was no significant difference in the systolic blood pressure increase on exercise between patients taking β blockers (23 (1.7%)) and those who were not (19.8 (2.0%)). There were significant differences in the resting and peak heart rates and the total exercise time between the two groups (table 4).

Table 4 Mean values (SE) for resting and peak heart rates and exercise time in patients taking β blockers and in those who were not

	β blockers	No β blockers	p value
Resting heart rate (beats/min)	68 (2)	90 (2)	<0.001
Peak heart rate (beats/min)	116 (2)	140 (2)	<0.001
Exercise time (min)	6.9 (0.3)	5.8 (0.3)	<0.01

Discussion

We have shown that the presence of exercise induced ST segment depression alone is a poor predictor of severe coronary disease because only 45% of 74 patients with significant ST segment depression had triple vessel disease shown by angiography. This accords with a recent study⁴ but not with earlier ones.^{5,6} We have demonstrated, however, that further analysis of the ST segment variables can predict more accurately the severity of coronary artery disease.

The absence of downsloping ST segment depression on exercise was the most specific indicator of the absence of triple vessel disease. Of the group with downsloping ST segment depression none had single vessel disease, 9.5% had double vessel disease, and 90.5% had triple vessel disease. Fourteen of the 33 patients with triple vessel disease, however, did not have downsloping ST segment depression. Given the widespread distribution of horizontal ST segment depression in patients with single and double vessel disease and triple vessel disease, further analysis of this configuration would be necessary to determine which ST segment characteristics are of diagnostic value. When exercise induced ST segment depression occurs in patients with triple vessel disease significant ST changes are likely to appear within the first stage of exercise, which was significantly earlier than for single or double vessel disease. Moreover, patients in whom the ischaemic ST segment persists for > 6 minutes after exercise are likely to have triple vessel disease. Subdivision of patients with horizontal ST segment depression into those with early onset and late recovery times allows triple vessel disease to be diagnosed with greater accuracy. Eleven (79%) of the 14 patients with triple vessel disease and horizontal ST segment depression had early onset and late recovery times compared with only four (16%) of the 25 with single or double vessel disease with horizontal ST segment depression. When these 14 patients were added to those patients in whom a downsloping configuration was a marker for triple vessel disease, 30 (90%) of the 33 patients with triple vessel disease and ST segment depression were correctly identified, with only 6 (15%) of the 39 patients with single and double vessel disease being misclassified.

Specific ST segment analysis can identify triple vessel disease more accurately than the simple presence of ST segment depression, which can only be regarded as a marker for the presence of myocardial ischaemia not its severity.

Recent studies have shown a significant association between a poor systolic blood pressure response on exercise and subsequent cardiac mortality in patients after myocardial infarction.^{2 7 8} This abnormal exercise response has been attributed to poor left ventricular function caused by a larger infarct.⁹ The results of our study suggest that a poor blood pressure response on exercise is associated with triple vessel disease. This group of patients had a significantly lower blood pressure increase than patients with single or double vessel disease. This observation accords with previous studies.^{4 10} Sullivan *et al* reported a significant association between a poor blood pressure response on exercise and multivessel disease.⁴ Further, they observed no significant difference in the resting ejection fraction between those patients with a good blood pressure response and those with an inadequate blood pressure response, suggesting that this inadequate response was not a product of poor left ventricular function. These results suggest that a poor blood pressure response may be a function of increased myocardial ischaemia.

No significant differences were seen in the peak heart rate attained on exercise by patients with single, double, and triple vessel disease. In patients with triple vessel disease, however, the increase in heart rate at the onset of significant ST segment depression was lower than in patients with single and double vessel disease. This suggests that patients with severe coronary artery disease increase their heart rate, and thus myocardial oxygen consumption, to a lesser extent before the onset of myocardial ischaemia.

A low maximum heart rate has been shown to be significantly associated with multivessel disease in patients with stable angina.¹¹ This association is not so clearly demonstrated in patients after myocardial infarction, mainly because there is left ventricular dysfunction. In contrast, Jennings *et al* reported a significant association between a high heart rate at peak exercise and subsequent cardiac mortality and suggested that this was indicative of left ventricular damage rather than the presence of myocardial ischaemia.²

The distribution of patients with significant ST segment depression on exercise was not significantly different between patients on β blockers and those who were not. Furthermore, there was no significant difference in the increase in systolic blood pressure on exercise between the two groups. These results

suggest that β blockers did not have a significant effect on the ischaemic responses obtained on exercise.

The aim of this study was to attempt to identify within the group of patients with ST segment depression those patients with triple vessel disease. Theroux *et al* reported a one year mortality rate of 25% in patients with exercise induced ST segment depression; only 2% of patients without ST segment depression died.¹ We studied only patients with ST segment depression or a poor haemodynamic response on exercise, and those who had symptoms or were young. Ideally coronary angiography would have been carried out on all patients to determine the distribution of vessel disease in patients with no ST segment depression. We did not consider this approach to be practical or ethical. The prevalence of triple vessel disease in the present study was similar to that previously reported.¹² Additionally, Akhras *et al* in a study of 61 patients undergoing exercise testing and coronary angiography after uncomplicated myocardial infarction found that 43 patients with multivessel disease had ST segment depression compared with only two patients with no ST segment depression.¹³ Furthermore, 89% of patients with triple vessel disease were found within the group with exercise induced ST segment depression.¹⁴

In an attempt to avoid the problems of differentiating between double and triple vessel disease, comparative studies have identified patients as having either single or multivessel disease (double and triple vessel disease).^{4 5} Our results have clearly shown that as groups, patients with single, double, and triple vessel disease behave quite differently in terms of their electrocardiographic and haemodynamic responses to exercise. A small proportion of patients with double vessel disease may, however, have exercise responses that resemble those of patients with triple vessel disease. Thus a clear distinction cannot be made between these patients and those with triple vessel disease—an indication of the difficulties of allocating some patients to separate coronary vessel disease groups.

This study has shown that symptom limited exercise testing early after a myocardial infarction is an effective diagnostic technique for identifying patients with severe triple vessel disease. Although we have shown that the presence of ST segment depression alone is a poor indicator of the presence of triple vessel disease, specific analysis of the ST segment changes together with an assessment of the haemodynamic response to exercise can more accurately identify a group of patients who may be at high risk. The simplicity of this approach may be of particular relevance to district hospitals where there

are adequate facilities for exercise testing but where access to angiographic techniques is restricted and more accurate identification of patients with suspected triple vessel disease is needed.

References

- 1 Theroux P, Waters DD, Halphen C, Debaisieux J, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;301:341-5.
- 2 Jennings K, Reid DS, Hawkins T, Julian DJ. Role of exercise testing after myocardial infarction in identifying candidates for coronary surgery. *Br Med J* 1984;288:185-7.
- 3 Bruce RA. Exercise testing of patients with coronary heart disease. *Ann Clin Res* 1971;3:323-32.
- 4 Sullivan ID, Davies DW, Sowton E. Submaximal exercise testing early after myocardial infarction: difficulty of predicting coronary anatomy and left ventricular performance. *Br Heart J* 1985;53:180-5.
- 5 Schwartz KM, Turner JD, Sheffield LT, et al. Limited exercise testing soon after myocardial infarction; correlation with early coronary and left ventricular angiography. *Ann Intern Med* 1981;94:727-34.
- 6 Fuller CM, Raizer AE, Verani MS, et al. Early post myocardial infarction treadmill stress testing; an accurate predictor of multi-vessel coronary disease and subsequent cardiac events. *Ann Intern Med* 1981;94:734-9.
- 7 Handler CE. Submaximal predischarge exercise testing after myocardial infarction; prognostic value and limitations. *Eur Heart J* 1985;6:510-7.
- 8 Fioretti P, Brower RW, Maarten L, et al. Prediction of mortality during the first year after acute myocardial infarction from clinical variables and stress test at hospital discharge. *Am J Cardiol* 1985;55:1313-8.
- 9 Grande P, Pedersen A. Myocardial infarct size and cardiac performance at exercise soon after myocardial infarction. *Br Heart J* 1982;47:44-50.
- 10 Starling MR, Crawford MH, Richards KL, O'Rourke RA. Predictive value of early postmyocardial infarction modified treadmill exercise testing in multivessel coronary artery disease detection. *Am Heart J* 1981;102:169-75.
- 11 Thayssen P, Möller M, Haghfelt T, Jagt T. Ventricular arrhythmias in relation to coronary artery stenosis and left ventricular performance. *Eur Heart J* 1982;3:35-41.
- 12 De Feyter PJ, van Eenige MJ, Dighton DH, Visser FC, De Jong J, Roos JP. Prognostic value of exercise testing, coronary angiography and left ventriculography 6-8 weeks after myocardial infarction. *Circulation* 1982;66:527-36.
- 13 Akhras F, Upward J, Scott R, Jackson G. Early exercise testing and coronary angiography after uncomplicated myocardial infarction. *Br Med J* 1982;284:1293-4.
- 14 Veenbrink Th WG, van der Werf T, Westerhof PW, Robles de Medina EO, Meijler FL. Is there an indication for coronary angiography in patients under 60 years of age with no or minimal angina pectoris after a first myocardial infarction? *Br Heart J* 1985;53:30-5.