Post-infarction exercise testing in patients under 55 years

Relation between ischaemic abnormalities and the extent of coronary artery disease

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SUMMARY Previous studies have suggested that the early post-infarction exercise test is useful in predicting the extent of coronary artery disease. The results of a heart rate limited exercise test three weeks after infarction and a symptom limited exercise test six weeks after infarction obtained by both standard 12 lead electrocardiograms and 16 lead precordial maps were compared in 100 consecutive survivors of acute myocardial infarction under 55 years of age. Exercise tests were defined as being positive on the basis of angina, ST segment depression \( \geq 1 \) mm in any electrocardiogram lead, or exertional hypotension. Multivessel disease, that is two or three vessel disease, was present in 60 patients, and three vessel disease in 22 patients. The sensitivity, specificity, and predictive value for multivessel disease of the three week test were 38\%, 83\%, and 76\% respectively; and results for the six week test were 55\%, 75\%, and 77\% respectively. Only 32\% of patients with three vessel disease were identified at the three week test, and 59\% at the six week test. Significantly more patients with multivessel and three vessel disease were identified by the symptom limited six week test. Precordial mapping offered no advantages over the standard 12 lead electrocardiogram in either the identification of patients with multivessel disease or the prediction of the distribution of coronary artery disease. Angina pectoris during the exercise test at six weeks was the single most useful predictor of multivessel disease. Multivessel disease was found in 27 (87\%) of the 31 patients with angina with or without ST depression during the test at six weeks compared with 33 (48\%) of the 69 patients who did not have angina during the test at six weeks.

Exercise testing in the early post-infarction period in patients under 55 years of age is of limited value in predicting the extent of coronary artery disease. It is, therefore, unreasonable to use such exercise tests to select patients for coronary arteriography after myocardial infarction. None the less angina pectoris occurring during a symptom limited exercise test six weeks after infarction is a strong predictor of multivessel disease, and coronary arteriography is recommended in these patients.

The major determinants of long term outcome after acute myocardial infarction are age,\(^1\)\(^-\)\(^3\) left ventricular function,\(^3\)\(^4\) and, in patients without severe left ventricular impairment, the extent of underlying coronary artery disease.\(^3\)\(^4\)\(^5\) An important aspect of the management of survivors of myocardial infarction is the identification of those patients at increased risk of subsequent cardiac events. A non-invasive means of predicting the extent of coronary artery disease would therefore be useful.

Treadmill exercise testing is safe in the early post-infarction period\(^6\) and several studies have examined its value in the prediction of the extent of coronary artery disease.\(^7\)\(^-\)\(^9\) In many of the studies sub-maximal exercise tests were performed within three
weeks of myocardial infarction, and significant numbers of patients with two and three vessel disease had negative tests.9-11 Because Starling et al have shown that some patients develop ST depression at six weeks but not at three weeks after infarction,12 a later maximal exercise test may detect some of these patients.

On the basis of results from previous studies the early post-infarction exercise test is being recommended as a filter for the selection of patients for coronary arteriography13,14 and their subsequent referral for early coronary artery surgery.7,15 Many of the studies upon which such recommendations are based have, however, included patients up to 65 or 70 years of age.8,9,16 It may not be appropriate to apply such data to the management of younger patients in whom prophylactic interventions such as coronary artery surgery are more likely to be considered.

The main purpose of the present study was to evaluate the relation between exercise induced myocardial ischaemia early after myocardial infarction and the extent of coronary artery disease in a group of younger patients. The study was prospective and of a consecutive group of patients under 55 years who were admitted to the coronary care unit and survived acute myocardial infarction. The study design allowed us to assess the importance of the timing and intensity of exercise by comparing an early submaximal exercise test with a later maximal exercise test. We also examined the value of precordial electrocardiographic mapping during exercise since Fox et al have demonstrated its ability to identify the presence of left main stem or proximal left anterior descending artery lesions.17

**Patients and methods**

**STUDY POPULATION**
The study population was drawn from a consecutive group of 184 patients with proven myocardial infarction under 55 years of age and admitted to our coronary care unit between October 1981 and February 1984 (Fig. 1). Acute myocardial infarction was diagnosed when a patient presented with a history of typical chest pain lasting at least 30 minutes with characteristic electrocardiographic changes, that is a sequential rise of ST segment, inversion of T waves, and appearance of new Q waves, or a rise in either creatine phosphokinase, lactate dehydrogenase, or aspartate aminotransferase to at least twice the upper limit of the normal range. Fourteen (7.6%) of the 184 patients died in hospital after the acute event and 70 (41%) of the survivors were excluded from the study for the reasons indicated in Fig. 1. Twelve patients were unable to exercise, nine for orthopaedic or neurological reasons and three because of left ventricular failure. Thirteen patients had other serious, non-cardiac diseases which prevented them participating in the study. Of the 45 patients excluded for administrative reasons, 22 patients refused to participate in the study, six lived away from the area and had been on holiday when they had their acute infarction, and 17 patients were missed during the course of the study. The study group therefore consisted of 100 patients.

**EXERCISE TEST**
All patients had a submaximal treadmill exercise test three weeks after infarction (mean 19.7 days, range 17-24 days) and a maximal treadmill exercise test six weeks after infarction (mean 42.7 days, range 35-50 days). A modified Bruce protocol was used for both tests. The submaximal three week test were terminated if (a) the patient developed limiting symptoms of chest pain, dyspnoea, or fatigue; (b) there was a sustained fall in systolic blood pressure of > 20 mm Hg from values attained earlier during exercise; (c) ventricular extrasystoles occurred in runs of three or more; (d) there was ST segment depression of > 4 mm, or (e) a heart rate of 130 beats/minute was achieved in the absence of other end points. The end points for the maximal six week test were the same except that the heart rate limitation was not applied. There were no complications.

All patients had both standard 12 lead electrocardiograms and 16 lead precordial maps recorded at rest, at peak exercise, and at 1, 3, and 5 minutes after exercise.

**CORONARY ARTERIOGRAPHY**
Coronary arteriography and left ventricular angiography were performed by the Judkins or Sones techniques in all patients a mean of three months after their acute myocardial infarction. The coronary arteries were viewed in multiple projections and left ventricular angiograms were recorded in both 30° right anterior oblique and either 60° left
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Fig. 2 Position of precordial map chest electrodes (from Fox et al.17). For analysis of distribution of coronary artery disease the precordial map was divided into anterior, inferior, and lateral regions.

DEFINITIONS

An exercise test was considered to be positive if (a) the patient developed angina pectoris; (b) there was horizontal or downsloping ST segment depression of >1 mm lasting 0.08 s after the J point of the QRS complex in any of the standard leads or leads of the precordial map; or (c) there was an inadequate blood pressure response to exercise shown by an increase of <10 mm Hg in systolic blood pressure over the resting value or a sustained fall in systolic blood pressure of >20 mm Hg from values attained earlier during exercise.

At coronary arteriography an important stenosis was defined as one in which there was a ≥50% reduction in luminal diameter of a major coronary artery in two orthogonal views. In other studies a reduction of ≥70% in luminal diameter was regarded as being important (see Table 3). Stenoses in major diagonal or obtuse marginal (lateral circumflex) branches were considered to constitute left anterior descending or left circumflex artery disease respectively. The term multivessel coronary artery disease refers to important disease in two or more major coronary arteries.

For analysis and comparison of our results with those of Fox et al.17 we subdivided the 16 lead precordial map into anterior, inferior, and lateral regions (Fig. 2). Their study demonstrated the associations (a) between ST segment depression in the first row of the precordial grid and the presence of important left main stem or proximal left anterior descending artery stenoses, (b) between ST depression in the anterior or inferior regions and the presence of important left anterior descending or right coronary artery stenoses respectively, and (c) between ST depression in all three regions and the presence of important three vessel disease.

STATISTICAL ANALYSIS

We used the $\chi^2$ test for group comparisons. McNemar’s test19 was used to evaluate the difference in exercise test results between three week and six week tests. The sensitivity, specificity, and predictive values of a positive and negative test to detect the presence or absence of multivessel disease were determined. Sensitivity was defined as the percentage of patients with multivessel coronary artery disease who had a positive test. Specificity was defined as the percentage of patients without multivessel coronary artery disease who had a negative test. The positive predictive value was defined as the percentage of patients with a positive test who had multivessel coronary artery disease. The negative predictive value was defined as the percentage of patients with a negative test who did not have multivessel coronary artery disease, that is those who had insignificant or single vessel disease.

RESULTS

CLINICAL CHARACTERISTICS

The mean age of the 100 patients in the study group was 46-6 years (range 32-54 years). There were 90 men and 10 women. Seven patients had had a previous myocardial infarction. The index infarction was anterior in 45 patients and inferior in 55 patients. Only three patients were taking beta blockers at the time of their three week exercise test and four patients at the time of their six week exercise test. No patient was taking digoxin.
Table 1  Exercise test responses at the three week and six week exercise tests derived from both standard 12 lead electrocardiograms and 16 lead precordial maps

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<thead>
<tr>
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<th>3 weeks</th>
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<tr>
<td>Positive test:</td>
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<tr>
<td>Angina and ST depression</td>
<td>16</td>
<td>11</td>
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<tr>
<td>Inadequate blood pressure and ST depression</td>
<td>6</td>
<td>12</td>
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<tr>
<td>Negative test</td>
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ANGIOGRAPHY

Five patients were found to have no important coronary artery disease, 35 patients had important single vessel disease, 38 patients had two vessel disease, and 22 patients had three vessel disease. Multivessel coronary artery disease was present in 60 patients. Only two patients had an important left main stem lesion; in one of these the left main stem was occluded. Twenty five patients had important disease of the proximal left anterior descending artery (that is proximal to the origin of the first septal artery). Of the 55 patients with inferior infarction, 34 (62%) had multivessel disease while 26 (58%) of the 45 patients with anterior infarction had multivessel disease. This difference was not statistically significant. At the time of their exercise test six weeks after infarction 38 patients gave a clinical history of angina on exertion. Multivessel disease was detected in 28 (74%) of these patients compared with 32 (52%) of the 62 patients without clinical angina (p < 0.05).

EXERCISE TEST

Table 1 lists the exercise test responses in all patients derived from data from both the standard 12 electrocardiogram leads and the 16 lead precordial map. Only 25 (66%) of the 38 patients with a clinical history of angina six weeks after infarction developed angina during their exercise test at six weeks. An additional six patients without clinical angina experienced angina during the exercise test at six weeks (Table 1). Angina during the exercise test at six weeks proved to be a useful predictor of multivessel coronary artery disease. Multivessel disease was found in 27 (87%) of the 31 patients who had angina alone or angina with ST depression at the six week exercise test compared with 33 (48%) of the 69 patients without angina at the six week exercise test. This difference is highly significant (p < 0.0005). Of the 19 patients with angina alone, 16 (84%) had multivessel disease and 8 (42%) of them had three vessel disease; and of the 12 patients with both angina and ST depression, 11 (92%) had multivessel disease, two (17%) having three vessel disease. Only four (36%) of the patients with ST depression alone had multivessel disease; and of the patients with an inadequate blood pressure response and ST depression there was one each with single, two, and three vessel disease.

Table 2 correlates the extent of coronary artery disease with the numbers of positive exercise tests at three weeks and six weeks after infarction. The results are presented separately for the 12 lead and 16 lead systems.

12 LEAD VERSUS 16 LEAD

At neither the three week nor the six week exercise test was 16 lead precordial mapping significantly better than the standard 12 leads in identifying those patients with multivessel disease. No patient with three vessel disease was identified by electrocardiographic mapping and not by the standard leads. Similarly no patient with a positive test on the standard 12 leads had a negative test on the precordial map. The specificity of the 16 lead system was slightly less at both three and six weeks because additional patients with single vessel disease had ST depression on the precordial map but not the standard 12 lead electrocardiogram on both occasions.

The precordial map was subdivided into anterior, inferior, and lateral regions (Fig. 2) to examine the relation between exercise induced ST depression in leads distant from those affected during the acute infarction and the extent of coronary artery disease. For comparison the standard 12 leads were also grouped as anterior (V1–V5), inferior (II, III, and aVF) and lateral (I, aVL, and V6). From data obtained at the six week exercise test important disease in the appropriate arteries (subtending electro-
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Two vessel disease

<table>
<thead>
<tr>
<th>3 week test</th>
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<td>+</td>
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Three vessel disease

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Multivessel disease

<table>
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Fig. 3  Comparison of the results of the three week and six week exercise tests in patients with two vessel disease (a), three vessel disease (b), and multivessel disease (c) using standard 12 lead data only. +, positive exercise test; −, negative exercise test.

cardiographic regions not affected by the acute infarction) was correctly predicted by precordial mapping in 17 (65%) of the 26 patients with ST depression and by standard electrocardiogram leads in 15 (58%). The difference between the two lead systems is not significant. The remaining nine patients (of the 26) with ST depression had either insignificant (two patients) or single vessel (seven patients) coronary artery disease. There were 25 patients with important proximal left anterior descending disease. In 10 patients the vessel was occluded and in 15 patients the vessel was significantly narrowed. In nine (60%) of the 15 patients with narrowed vessels the index infarction was inferior and the precordial electrocardiogram leads had no Q waves or resting ST segment abnormalities. Only one (11%) of these nine patients developed ST depression in the first row of the precordial grid. Only one of the two patients with important left main stem disease presented with inferior infarction and he developed neither angina nor ST depression at either of the two exercise tests. The 16 lead precordial map was not therefore useful in predicting the presence of left main stem or proximal left anterior descending artery disease.

Because the 16 lead precordial map did not identify more patients with multivessel disease than the 12 standard leads, we based the comparison between the 3 week and 6 week exercise tests on data obtained with the standard 12 leads only.

Three weeks versus six weeks

The sensitivity, specificity, and predictive value of a positive submaximal exercise test 3 weeks after infarction for patients with multivessel disease are 38%, 83%, and 76% respectively. The predictive value for three vessel disease is only 24%, with 15 (68%) of patients with three vessel disease having a negative exercise test. The negative predictive value of the three week test is 46%.

The sensitivity, specificity, and predictive value of a positive maximal exercise test six weeks after infarction for patients with multivessel disease are 55%, 75%, and 77% respectively. The predictive value for three vessel disease is only 30%, with nine (41%) of patients with three vessel disease having a negative exercise test. The negative predictive value of the six week test is 53%.

Only 23 (38%) of the patients with multivessel disease were identified at the three week test compared with 33 (55%) at the six week test (p < 0.05) (Fig. 3c). Significantly more patients with three vessel disease were identified at the maximal six week test (p < 0.05) (Fig. 3b). The difference was not significant for patients with two vessel disease (Fig. 3a).

Discussion

The extent of underlying coronary artery disease is one of the important determinants of long term prognosis in survivors of an acute myocardial infarction.3–5 Knowledge of its extent in individual patients would thus help greatly in the planning of long term management.

Although coronary arteriography is safe and carries very little risk,6 its widespread use in all survivors of acute myocardial infarction is impractical. Alternative, cheaper non-invasive means of predicting the extent of coronary artery disease have therefore been sought. These could be more widely applied and used as a filter to select those patients who should proceed to coronary arteriography. Treadmill exercise testing is now widely used in this context10 and forms a routine part of post-infarct management in many centres.

Studies examining the ability of the early post-infarction exercise test to predict the extent of coronary artery disease have produced conflicting results.7–10 (Table 3). The sensitivity of exercise testing for identifying multivessel disease varies from 56% to 96%, the specificity from 53% to 94%, and the predictive value of a positive test from 74% to 98%. Several factors might explain the differing results. Different populations have been investigated, the timing of the exercise tests has differed, different exercise protocols have been used, and the end points have differed, some being heart rate limited9–11 and others symptom limited.7 8 The definition of an important coronary artery stenosis has also differed. The values of an early submaximal and a later maximal exercise test in predicting the extent of coronary artery disease in the same group
of patients have not been compared before.

We chose to investigate patients under 55 years because many centres still perform routine coronary arteriography on younger patients after myocardial infarction and also because prophylactic interventions are more likely to be considered in this age group.

12 LEAD VERSUS 16 LEAD

In their original study using precordial mapping in a small group of patients Fox et al suggested that 16 lead precordial mapping may show areas of ischaemia inaccessible to the standard 12 leads. After infarction precordial mapping might aid identification of some of the appreciable number of patients with multivessel coronary artery disease and a negative exercise test on the conventional electrocardiogram leads. The present study, however, has shown that the 16 lead system offers no advantages over the standard 12 leads in identifying these patients. We were also unable to confirm the findings of Fox et al of a correlation between ST segment changes within specific regions of the precordial grid and the distribution of coronary artery disease. Although Fox et al were able to identify all patients, in a group suffering from stable angina, with significant left main stem or proximal left anterior descending disease, most of our patients with such lesions did not have ST depression on exercise.

The major reason for the differing results undoubtedly relates to the study populations investigated. Our patients had recently sustained an acute myocardial infarction and many (usually those with anterior infarcts) had electrocardiographic abnormalities at rest and developed ST segment elevation on exercise. Parts of the precordial grid were therefore excluded from developing ST segment depression during exercise. In addition the development of ST elevation on exercise may have prevented the development of ST depression in the reciprocal territory by generating an opposing force to the ischaemic vector.

Since the 16 lead precordial map offers no advantages over the standard 12 leads the subsequent discussion is based on results using the standard 12 leads only.

THREE WEEKS VERSUS SIX WEEKS

We have demonstrated that a maximal exercise test six weeks after infarction is significantly better than a submaximal exercise test three weeks after infarction in identifying patients with multivessel disease (Fig. 3c, p < 0.05) and three vessel disease (Fig. 3b, p < 0.05), but not two vessel disease (Fig. 3c, p = NS). No patient with three vessel disease had a positive exercise test at three weeks that became negative at six weeks (Fig. 3b). Neither exercise test was highly sensitive or specific when the data were analysed on the basis of a significant reduction in luminal diameter being ≥50% or ≥70% (Table 3).

Several factors may explain the differences in results between this and previously published studies (Table 3). We studied consecutive patients who fulfilled no specific criteria except that they survived their acute myocardial infarction, agreed to participate in the study, and had no other serious non-cardiac disease. Others, however, have studied selected study populations. They have included consecutive patients fulfilling specific criteria, non-consecutive patients with symptoms or an abnormal haemodynamic response to exercise, or survivors of an uncomplicated myocardial infarction. The age of the subjects investigated may also be important. Most previous studies, except that of Akhras et al, have included older patients in whom the frequency of both previous myocardial infarction (which has been associated with a higher prevalence of multivessel disease) and multivessel disease are higher (Table 3). The sensitivity of exercise testing might therefore be expected to be greater. Another important factor may be the exercise protocol used. Two previous studies have used a modified Bruce protocol to a submaximal end point at 2–3 weeks after infarction but in an older

### Table 3

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient's age (yr) (n)</th>
<th>Previous MI</th>
<th>Timing</th>
<th>Exercise test</th>
<th>Protocol</th>
<th>End point</th>
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<td>Akhras et al 1982</td>
<td>&lt;55 (61)</td>
<td>—</td>
<td>2–3 wk</td>
<td>Bruce</td>
<td>Maximal</td>
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<td>2 wk</td>
<td>Naughton</td>
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<td>25%</td>
<td>13 days</td>
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<td>18–22 days</td>
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<td>29–64 (62)</td>
<td>15%</td>
<td>7–23 days</td>
<td>Modified Naughton</td>
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<tr>
<td>Present study</td>
<td>&lt;55 (100)</td>
<td>7%</td>
<td>6 wk</td>
<td>Modified Bruce</td>
<td>Submaximal</td>
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group of patients. Their figures for sensitivity in detecting multivessel disease were similar to those obtained at the maximal six week exercise test in our patients and similar numbers of patients with negative exercise tests had multivessel disease (Table 3).

It was difficult to understand the pronounced differences in results between this study and that of Akhras et al in patients of a similar age. The major differences between the studies are the differing frequency of multivessel disease, their use of symptom limited exercise testing at 2–3 weeks after infarction, and their method of analysis which was based on ST segment changes only. This latter point may have little bearing on the differing results since heart rate limited and symptom limited exercise testing three weeks after infarction have been shown to have a similar yield of ST segment depression although this was in different groups of patients. Use of such a method of analysis in the present study would have resulted in much poorer figures for sensitivity and specificity.

The results of the present study once again stress the importance of angina pectoris as a variable identifying patients with multivessel disease. Multivessel disease was found in 74% of patients with a clinical history of angina six weeks after infarction, confirming the findings of Alijarde et al, and in 90% of patients with exercise induced angina at the maximal six week exercise test.

As in previous studies considerable numbers of patients with multivessel disease or three vessel disease had negative exercise tests. In view of recently published data these patients may represent a subgroup with a better prognosis than the extent of their coronary artery disease would suggest.

We were unable to confirm previously published data suggesting a higher incidence of multivessel disease in patients with inferior infarction. The frequency of multivessel disease in patients with anterior or inferior infarction did not differ significantly, thus confirming the findings of Veenbrink et al and Roubin et al.

CONCLUSIONS
The present study demonstrates that early exercise testing after acute myocardial infarction in patients under 55 years is of limited value in predicting the extent of coronary artery disease. Precordial mapping offers no advantages over the standard 12 electrocardiogram leads in either the identification of patients with multivessel disease or in the prediction of the distribution of coronary artery disease. The symptom limited six week exercise test has been shown to identify significantly more patients with either multivessel disease (p < 0.05) or three vessel disease (p < 0.05) than the earlier submaximal test. Many patients with coronary artery disease known to have an adverse effect on prognosis are, however, not identified. We therefore suggest that it is unreasonable to use early exercise testing as a guide to the selection of patients for coronary arteriography after acute myocardial infarction.

Angina pectoris either as a presenting symptom early after infarction or when it occurs during exercise testing (with or without ST segment depression) is a strong predictor of multivessel disease. Because these patients may represent a high risk group for subsequent cardiac events we recommend coronary arteriography in this group.

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