Prognostic value of symptom limited versus low level exercise stress test before discharge in patients with myocardial infarction treated with thrombolytics

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Abstract

***Objective*—To evaluate the benefits and risks of symptom limited exercise testing versus low level exercise testing soon after a thrombolytic treated acute myocardial infarction.**

***Design and patients*—98 patients (71 men, 27 women), mean (SD) age 64 (9) years (range 45–75 years), were investigated 5–8 days after admittance to hospital. An ergometer cycle test was used, starting at 30 W with 10 W increments per minute. Each exercise test was interpreted at the symptom limited end point and a low level end point, which was defined as the point at which the patient rated exhaustion as 13 on the 6–20 point Borg scale for rating perceived exertion.**

***Setting*—A university hospital.**

***Results*—75 of the 98 patients were able to perform a predischarge exercise test. Of the remaining 23 patients who could not perform an early exercise test (because of unstable angina, heart failure, or thrombus detected at echocardiography), five died or had a myocardial infarction and six underwent bypass surgery or percutaneous transluminal coronary angioplasty (PTCA) during a follow up period of one year. There were no complications related to the symptom limited exercise tests. The test results were positive in 15 patients at the low level end point and in 39 patients ($p < 0.001$) at the symptom limited end point. During a follow up period of one year, six of the 75 patients died or had a myocardial infarction. Two of these six patients had a positive low level exercise test and four had a positive symptom limited exercise test. Twenty three of the 75 patients who performed an exercise test had a cardiac event within one year (death, myocardial infarction, bypass surgery or PTCA); of these, 19 had a positive symptom limited exercise test and nine had a positive low level exercise test ($p = 0.025$). Four of the 36 patients with a negative symptom limited test suffered cardiac events within a year (two patients had a myocardial infarction and two had bypass surgery).**

***Conclusion*—Symptom limited exercise testing soon after thrombolytically treated myocardial infarction will identify more patients with exercise induced ST depression or chest pain than a low level test, and seems safe. A negative symptom limited test has a better negative predictive value (11% risk of an event within a year) than a negative low level (25% risk of an event within a year).**

(*Heart* 1999;**82**:199–203)

Keywords: exercise stress test; myocardial infarction; prognosis; thrombolysis; risk stratification

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Accepted for publication
9 February 1999

The guidelines of the American College of Cardiology[1] suggest that a symptom limited exercise test is done 14–21 days after infarction or, alternatively, that a low level exercise test is performed before discharge and then a symptom limited exercise test 6–8 weeks after infarction. A predischarge exercise test after myocardial infarction is done for risk stratification, for estimating functional capacity and prescribing activity, as well as to evaluate medical treatment.

Exercise test predictors of an adverse outcome in postinfarction patients include ST depression, especially if accompanied by symptoms, low exercise capacity, and an inadequate blood pressure response to exercise. In some, but not all, studies in the prethrombolytic era exercise induced ST depression was an important predictor of acute myocardial infarction or death. The positive predictive value of predischarge non-invasive testing has been reported to be lower in thrombolytically treated patients.[2] In the GISSI-2 study,[3] symptomatic ST depression, but not silent ST depression, was an independent predictor of cardiac mortality. The value of exercise testing for risk stratification after acute myocardial infarction in patients treated with a thrombolytic agent has been questioned.[4]

Whether a symptom limited test yields more ischaemic responses and has a better predictive value than a low level test has been debated. A study done before the introduction of thrombolysis showed no difference in ischaemic responses between exercise tests at low heart rates and symptom limited tests,[5] whereas Juneau and colleagues[6] found, in a mixed patient group, more ischaemic responses in symptom limited tests.

This study compares the prevalence of abnormal responses to low level and symptom limited exercise tests in patients with a recent, thrombolytically treated, acute myocardial infarction and assesses the ability of the two tests to predict future cardiac events.

Table 1 Borg scale for rating perceived exertion.[7]

Level of exertion	*Value*
Very, very light	6
	7
	8
Very light	9
	10
Light	11
	12
Somewhat hard	13
	14
Hard	15
	16
Very hard	17
	18
Very, very hard	19
	20

Methods

The inclusion criteria were: acute myocardial infarction treated by thrombolysis at Söder Hospital—the diagnosis was supported by a typical history of chest pain, ST elevation or left bundle branch block on ECG, and a typical pattern of enzymatic leakage; age > 45 and < 76 years old; and, for logistic reasons, only patients admitted to the coronary care unit on Sunday, Monday, and Tuesday. All patients gave their verbal informed consent.

The exclusion criteria were: previous acute myocardial infarction treated by thrombolysis within the previous three months; indication for acute coronary angiography/intervention; second or third degree atrioventricular block; clinical signs of severe heart failure (Killip 3–4); and other illness with a severe prognosis. The exclusion criteria were mainly set to exclude patients who might find it difficult to complete the study protocol. The study was approved by the ethics committee of the hospital.

SUBJECTS AND STUDY DESIGN

The patients in the study were enrolled between May 1994 and November 1996. One hundred and ninety six patients met the inclusion criteria, 89 of whom met at least one of the exclusion criteria, and ultimately 107 (78 men, 29 women) entered the study. Their mean (SD) age was 64 (9) years (range 45–75 years). The men were on average five years younger than the women (63 (9) *v* 68 (7) years).

EXPERIMENTAL PROTOCOL

The patients performed a symptom limited ergometer cycle exercise stress test 5–8 days after admission to the hospital. ECGs were recorded with six standard limb and six precordial leads and were monitored before exercise, continuously during exercise, and up to 10 minutes after completion of the exercise test. Blood pressures were recorded before and every minute during exercise. The initial workload was 30 W with 10 W increments every minute. The patients rated their level of exhaustion on the 6–20 point Borg scale for rating perceived exertion (table 1),[7] and chest pain (if any) was rated on the 0–10 point Borg scale. End points for exercise were: exhaustion (16–17 on the Borg scale of rated perceived exertion, but 15 for patients over 70 years of age); moderate chest pain (3–4 on the Borg scale), severe arrhythmia; > 10 mm Hg drop in blood pressure; or > 2 mm ST depression. The 6–20 point Borg scale rating perceived exertion can be used clinically to determine intensity of exercise.[7] The scale is constructed so that for a middle aged subject, the rated value multiplied by 10 corresponds roughly to heart rate during exercise on cycle ergometer. β Receptor blockade changes the heart rate response to exercise but not the perceived exertion in a major way.

For an approximate comparison between treadmill exercise and bicycle exercise, for a subject weighing 70 kg: 25 W on a bicycle ergometer corresponds to 1.7 miles per hour, 0% grade in the standard Bruce protocol (2–3 METS); 75 W corresponds to 1.7 miles per hour, 10% grade in the standard Bruce protocol (5 METS); and 125 W corresponds to 2.5 miles per hour, 12% grade in the standard Bruce protocol (7 METS).

Each exercise test was interpreted at the symptom limited end point and at a low level end point. The low level end point was defined as the point when the patient rated exertion at 13 on the 6–20 Borg scale.

The test result was considered positive if at least a 1 mm horizontal or downsloping ST segment was measured in at least two precordial leads 60 ms after the J point (or at least 0.1 mV additional ST depression if preexisting ST depression was noted), if the patient developed typical chest pain during or immediately after exercise, or if the blood pressure fell > 10 mm Hg (only one patient had a positive exercise test because of a fall in blood pressure alone). Poor blood pressure response (< 30 mm Hg increase from resting value) and low exercise capacity (arbitrarily chosen as < 1 W/kg) were not considered positive tests, but the results are presented separately.

STATISTICS

Data are expressed as mean (SD). Continuous variables were analysed using Student's *t* test. Categorical variables were analysed using the χ^2 test. Differences were considered significant at $p < 0.05$.

Results

Of the 107 patients included in the study, seven withdrew their consent and two had a lethal reinfarction before the exercise test. Seventy five of the remaining 98 patients performed an exercise test, while 23 patients could not undertake an exercise stress test 5–8 days after admittance to hospital. The reasons for this were unstable angina, uncontrolled heart failure, or the presence of an apical thrombus at echocardiography. The patients who could not perform an exercise test had a lower left ventricular ejection fraction than those who could do a test. Descriptive data of the patients who could and could not do a predischarge exercise test are shown in table 2.

Table 2 Comparison between patients that could and could not perform exercise stress test

	Exercise stress test (n = 75)	*No exercise stress test (n = 23)*
Age (years)	63 (9)	66 (9) p = 0.2
Left ventricular ejection fraction (nuclear angiography)(%)	45 (9)	39 (13) p = 0.007
Aspartate aminotransferase (μkat/l)	5.5 (3.8)	7.5 (6.3) p = 0.04
Number of patients using β blockers	70 (93%)	19 (83%)
Number of patients using calcium channel blockers	5 (7%)	2 (9%)
Number of patients using nitrates	31 (41%)	8 (3%)
Number of patients using ACE inhibitors	23 (31%)	17 (74%)

EXERCISE TEST RESULTS

The test results are presented in table 3.

Fifty two patients had Q wave (31 inferior, 21 anterior) and 22 non-Q wave (seven inferior, 11 anterior) infarctions. One had a left bundle branch block. In four cases the localisation of the infarction could not be determined from the ECG. Eleven of the 31 patients with inferior Q wave infarctions and 17 of the 21 patients with anterior Q wave infarctions had ST segment elevation at rest.

Table 3 Anthropometric data, exercise capacity, heart rate, and blood pressure responses to exercise in 75 patients performing a symptom limited cycle exercise test 5–8 days after thrombolytically treated acute myocardial infarction

	All subjects (n = 75)
Age (years)	64 (9)
Weight (kg)	77 (15)
Resting heart rate (beats/min)	71 (12)
Maximal heart rate during exercise (beats/minute)	115 (18)
Resting blood pressure (mm Hg)	134 (25)
Maximal blood pressure during exercise (mm Hg)	165 (29)
Increase in blood pressure during exercise (mm Hg)	34 (18)
Maximal exercise capacity on cycle ergometer (W)	93 (25)
Exercise capacity per kg (W/kg)	1.23 (0.29)

Table 4 Comparison of patients with positive versus negative symptom limited exercise stress tests 5–8 days after thrombolytically treated myocardial infarction. Five tests were inconclusive; there were no cardiac events in this group

	Positive tests (n=39) (29 men, 10 women)	*Negative tests (n=31) (22 men, 9 women)*	*p Value*
Age (years)	63 (9)	64 (9)	0.7
Left ventricular ejection fraction (%)	45 (9)	47 (10)	0.9
Maximal exercise capacity (W)	91 (26)	96 (22)	0.4
Resting heart rate (beats/min)	72 (14)	69 (15)	0.6
Maximal heart rate (beats/min)	116 (14)	115 (30)	0.8
Q wave infarction anterior/inferior	9/20	9/11	
All events	19	4	
Non-fatal acute myocardial infarction	3	2	
Fatal acute myocardial infarction	1	0	
CABG	7	2	
PTCA	8	0	

CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.

Table 5 Results of positive symptom limited versus positive low level cycle ergometer exercise tests performed 5–8 days after thrombolytically treated acute myocardial infarction.

	Symptom limited end point	*Low level end point*
ST segment depression (> 1 mm)	17	10
Chest pain	15	6
ST segment depression and chest pain	5	4
Positive test (ST segment depression/chest pain/BP fall)	39	15
Inadequate BP response (< 30 mm Hg increase)	33	
Low exercise level at symptom limited endpoint (< 1 W/kg)	18	

Values are number of patients. Three of the patients developed chest pain after exercise and were considered negative in low level exercise. BP, blood pressure.

Reasons for stopping the exercise tests were exhaustion in 56 cases (tired legs in 20 cases, shortness of breath or general fatigue in the other cases), chest pain in seven cases, a drop in systolic blood pressure in five cases, and changes in ECG in seven cases (five of them ST depression $\geq$ 2 mm and an extreme ST elevation in two cases). One patient had atrial fibrillation; all the others had sinus rhythm. None had serious arrhythmia during or after exercise.

Thirty three patients had a systolic blood pressure increase of < 30 mm Hg from the resting value during exercise and 15 patients had a systolic blood pressure increase of < 20 mm Hg during exercise.

Twenty two patients had an exercise induced ST depression in precordial leads and five of these also had chest pain. Only three of the 21 patients with an anterior Q wave had an ST depression. A total of 20 patients had chest pain during or after exercise. Only one test was considered positive because of a drop in blood pressure alone (the other patients with blood pressure drops also had chest pain or ST depression). The results of positive versus negative tests are presented in table 4. In five patients, ST changes were considered inconclusive because of isolated inferior ST segment depression in three cases and left bundle branch block or bifascicular block in two cases. For statistical evaluation, these tests were considered negative.

Fifteen of the 39 patients with positive symptom limited exercise tests had positive tests at the lower end point. Three patients developed chest pain after exercise and were considered negative at the lower end point. The results are presented in table 5.

CARDIAC EVENTS

There were 34 cardiac events within a year. Four patients died and seven had a myocardial infarction. Ten patients had percutaneous transluminal coronary angioplasty (PTCA) and 13 had bypass surgery. There were 23 events in the 75 patients who had performed an exercise test and 11 events in the 23 patients who did not perform an early exercise test (p = 0.13).

The ability of symptom limited versus low level exercise tests to predict future events are shown in table 6.

Positive symptom limited test

Nineteen of the 39 patients who had a positive test had events within one year. One of these patients had a fatal reinfarction, three suffered a new acute myocardial infarction, seven underwent bypass surgery, and eight had PTCA.

Negative symptom limited exercise test

Four of the 36 patients who had a negative or inconclusive exercise test had events within one year. Two patients suffered a new acute myocardial infarction and one of them underwent bypass surgery; another two patients also underwent bypass surgery.

Positive low level exercise test

Nine of the 15 patients with a positive low level test suffered cardiac events. One patient had a fatal reinfarction and one suffered a new acute myocardial infarction. Three patients underwent bypass surgery and four had PTCA.

Negative low level exercise test

Fourteen of the 57 patients with a negative low level test or with ST depression in inferior leads only, left bundle branch block or bifascicular

Table 6 Ability of symptom limited versus low level exercise tests to predict events within one year

	Positive symptom limited test (n = 39)	*Negative or inconclusive test (n = 36)*	*Positive low level test (n = 15)*	*Negative (or inconclusive) low level test (n = 60)*	*No exercise test (n = 23)*
All events	19	4	9	14	11
Hard events (Death/AMI)	4 1/3	2 0/2	2 1/1	4 0/4	5 3/2
Soft events (CABG/PTCA)	15 7/8	2 2/0	7 3/4	10 6/4	6 4/2

Three of the patients with reinfarction also underwent an intervention such as CABG or PTCA. Five tests were inconclusive at the symptom limited end point. There were no cardiac events in the patients with inconclusive tests. AMI, acute myocardial infarction.

block had cardiac events. Four patients had a new acute myocardial infarction, six underwent bypass surgery, and four had PTCA.

The test results were positive in 39 patients at the symptom limited end point and in 15 patients at the low level end point ($p = 0.006$). Nineteen of the patients who could perform an exercise test and had a cardiac event within a year had a positive symptom limited exercise test, and nine of them had a positive low level exercise test ($p = 0.025$).

Poor blood pressure response

Of the 33 patients with an increase in systolic blood pressure of < 30 mm Hg, two suffered a reinfarction (one fatal), five had bypass surgery, and five had PTCA. Twenty one of these patients had positive symptom limited exercise tests—that is, ST segment depression, chest pain, or both.

Low exercise capacity

Sixteen patients had low exercise capacity (< 1 W/kg) and seven of them had cardiac events. One patient had a fatal reinfarction, three had acute myocardial infarctions, one had bypass surgery, and two patients had PTCA. Five of the seven had positive exercise tests.

No exercise

Eleven of the 23 patients who did not exercise had cardiac events within one year. Three patients had a fatal reinfarction, two had acute myocardial infarction (one also underwent bypass surgery), four had bypass surgery, and two had PTCA.

Discussion

We have performed symptom limited exercise stress tests in 75 patients 5–8 days after a thrombolytically treated myocardial infarction and compared the symptom limited test results with the low level test results of these patients. We found that there were more ischaemic responses at the symptom limited end point than at the low level end point. The results are similar to those in studies including patients treated or not treated with thrombolytic agents.[6 8]

We chose a low limit end point based on the patients' rated exhaustion, rather than using a percentage of the age predicted heart rate, as the majority of the patients were being treated with β blocking agents which influence the heart rate response to exercise.

Mortality has decreased to 3–4 % within one year after acute myocardial infarction in patients treated with thrombolysis or coronary interventions during hospitalisation (coronary angioplasty or bypass surgery).[9] The decrease in one year mortality in patients receiving thrombolytic treatment has been explained by smaller infarct size and less likelihood of three vessel disease. The predictive value of ST segment depression in recent studies is reduced as revascularisation intervention procedures are often performed in patients showing ischaemic responses to exercise, and many patients also undergo coronary angiography instead of exercise testing.[1] The value of exercise testing for risk stratification after acute myocardial infarction in patients treated with thrombolytic agents has been questioned.[4]

In our study, few patients underwent acute coronary intervention procedures and the number of deaths within a year was also higher (although non-significantly) than the expected 3–4%. The present study thus provides an opportunity to evaluate the prognostic value of exercise testing.

About 75% of the patients could perform an exercise stress test 5–8 days after acute myocardial infarction. The most common reasons for not cycling were unstable angina, heart failure, or the presence of apical thrombus at echocardiography. As in other studies,[10–12] not being able to perform a predischarge exercise stress test was predictive of a poor outcome. Half of the patients who could not perform an early exercise stress test in our study had cardiac events within one year, three of them fatal.

Twenty three of the 75 patients who performed an exercise test had cardiac events (death, acute myocardial infarction, bypass surgery, PTCA) within one year. Among them, there were six hard events (death or acute myocardial infarction) and 17 patients underwent revascularisation.

An abnormal systolic blood pressure response has been reported to be a marker of a poor outcome. In 12 of the 33 patients with a poor blood pressure response who had cardiac events within a year, 10 also had positive symptom limited exercise tests. A poor blood pressure response or the combination of a positive test and a poor blood pressure response was not a better predictor of outcome in our study than exercise induced ST depression and chest pain. This may be because the majority of patients were being treated with β blocking agents which might influence the blood pressure response.

Reduced exercise capacity is another marker of a poor outcome. In our study, seven of 14 patients with a poor exercise capacity had a cardiac event within one year, and five of them also had a positive symptom limited test.

The symptom limited test had a better predictive value than the low level test. More than half of the patients with a positive low level test had cardiac events within one year, but the positive low level test had low sensitivity and "missed" 10 of the 23 events. Nearly half of the patients with a positive symptom limited test suffered cardiac events within a year. The symptom limited tests identified twice the number of patients with exercise induced ischaemia as the low level test.

As the results of the exercise stress tests were used for clinical decision making, it is not surprising that the patients with positive exercise tests were more likely to undergo revascularisation than other patients while, on the other hand, there were few cardiac events among the patients with a negative test. The negative predictive value of a negative symptom limited test was considerably higher than that of a negative low level test. For the patients with a negative symptom limited test, the risk of a cardiac

event within one year was only 11%, compared to a 25% risk in patients with a negative low level test.

The advantage of an earlier test is the possibility of early risk stratification and the possibility of starting cardiac rehabilitation earlier in a large group of patients. Four of the events that occurred in patients that could undertake an exercise test occurred within six weeks after the myocardial infarction (compared to 10 events in the group that could not undertake an exercise test). A symptom limited test is more accurate in estimating the patients' functional capacity when prescribing activity. Patients with a negative symptom limited test therefore do not have to be unnecessarily limited in their activities and cardiac rehabilitation could start earlier.

The symptom limited exercise test was safe in all 75 patients in this study, as in the study by Jain and colleagues which included 150 patients.[8]

In conclusion, a symptom limited test soon after myocardial infarction seems to be safe and identifies more patients at risk for recurrent events. The risk for a cardiac event within one year is low in patients with a negative symptom limited exercise test. The prognostic value of exercise testing appears to be maintained in patients treated with thrombolytic agents after an acute myocardial infarction.

We thank Gun Wedeen and Solveig Andersson for their important contributions to the study. This study was supported by grants from the Swedish Heart Lung Foundation, the Swedish Society of Physicians, and the Karolinska Institute.

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