COOPERATIVE STUDIES

Prognostic Significance of the Treadmill Exercise Test Performance 6 Months After Myocardial Infarction

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A submaximal treadmill exercise test performed before hospital discharge after an uncomplicated myocardial infarction is often utilized to estimate prognosis and guide management, but there is little experience with a *maximal* exercise test performed 6 months after infarction to identify prognosis later in the convalescent period. The performance characteristics during an exercise test 6 months after myocardial infarction were related to the development of death, recurrent nonfatal myocardial infarction and coronary artery bypass surgery in the subsequent 12 months (that is, 6 to 18 months after infarction) in 473 patients. Mortality was significantly greater in patients who exhibited any of the following: inability to perform the exercise test because of cardiac limitations, the development of ST segment elevation of 1 mm or greater during the exercise test, an inadequate blood pressure response during exercise, the development of any ventricular premature depolarizations during exercise or the recovery period and inability to exercise beyond stage I of the modified Bruce protocol. By utilizing a combination of four high risk prognostic features from the exercise test, it was possible to stratify patients in terms of risk of mortality, from 1% if none of these features were present to 17% if three or four were present.

Recurrent nonfatal myocardial infarction was predicted by an inability to perform the exercise test because of cardiac limitations, but not by any characteristics of exercise test performance. Coronary artery bypass surgery was associated with the development of ST segment depression of 1 mm or greater during the exercise test. Although clinical evidence of angina and heart failure 6 months after infarction was predictive of subsequent mortality among all survivors, among the low risk group without severely limiting cardiac disease, the exercise test provided unique prognostic information not available from clinical assessment alone. Therefore, a maximal exercise test performed 6 months after myocardial infarction is a valuable, noninvasive tool to evaluate prognosis. It provides information that is independent of and additive to clinical evaluation performed at the same time.

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The treadmill exercise test performed before hospital discharge after an uncomplicated myocardial infarction is widely used to estimate prognosis and aid in management decisions (1,2). Prognostic information can be gleaned from criteria including exertional ST segment depression or elevation (3–12), exercise duration (13–16), blood pressure response to exercise (16–18), the development of ventricular premature depolarizations (16) and the occurrence of angina pectoris (16,19). Integration of information derived from the predischarge exercise test with that derived from the

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patient's hospital course improves the assessment of prognosis (3,11,12,14,16,20). An exercise test is often repeated 6 to 8 weeks after the infarction when the myocardial scar has presumably matured, using a maximal effort exercise protocol to identify high risk patients (4,5,10,21,22).

However, the value of an exercise test performed later in the convalescent phase (6 months or more) after infarction is not clear. Although cardiac morbidity and mortality are maximal in the first 6 months after infarction (23–27), identification of patients who remain at increased risk, 6 months after the acute event would be useful. We therefore evaluated the relation between performance during an exercise test 6 months after infarction and morbidity and mortality during the following year. The prognostic value of the results of the test were compared with the prognostic value of clinical characteristics at 6 months after infarction to determine whether the test provided independent useful information.

Methods

Study group. The patients studied were a subgroup of those enrolled in the Multicenter Investigation of the Limitation of Infarct Size (MILIS), which was designed to determine the effect of the administration of propranolol or hyaluronidase on the size of acute myocardial infarction. The MILIS protocol has been described previously (28). Patients were eligible for enrollment in MILIS if they were younger than 76 years of age, had at least 30 minutes of pain typical of myocardial ischemia and demonstrated electrocardiographic criteria of acute myocardial ischemia or evolving infarction (new Q waves greater than 30 ms in width and 0.2 mV or greater in depth or ST segment elevation or depression, or both, of 0.1 mV or greater in at least two related leads), left bundle branch block or idioventricular rhythm. Exclusion criteria, guidelines for standard care and procedures for the administration of hyaluronidase or propranolol have been reported (28).

As part of the MILIS protocol, all patients performed an exercise test 6 months after myocardial infarction if they were physically capable of performing the test and if they and their physician consented. The test was incorporated into the design of MILIS so that the long-term functional consequences of pharmacologic interventions implemented at the time of the index infarction could be assessed. Patients were eligible for this data bank study only if myocardial infarction had been confirmed and they survived for at least 6 months.

Data collection. Patients were evaluated 6 months after infarction with a detailed interval history and physical examination and an exercise test performed according to a modified Bruce protocol (29). The test was omitted if the patient or the patient's physician did not provide consent or if any of the following cardiac limitations were present: reinfarction within the previous 3 months, unstable angina or extremely limiting angina pectoris occurring more than once daily despite medical treatment or severely limiting the patient's activities, or both, New York Heart Association class III or IV congestive heart failure (defined by history, a gallop rhythm and rales on chest examination), high grade ventricular ectopic activity (≥6 ventricular premature polarizations per minute, couplets, ventricular tachycardia or multifocal origin) and second or third degree atrioventricular block. Patients were also excluded if they had a noncardiac physical limitation such as an acute systemic illness or a major musculoskeletal impairment.

Patients exercised on the treadmill until they were limited by symptoms, developed a decrease in the systolic arterial pressure of 10 mm Hg or greater, high grade ventricular ectopic activity or conduction disturbances (as defined previously) or attained 90% or more of the maximal predicted heart rate for age and maintained it for 1 minute. Target heart rates were those recommended by the American Heart Association (30). Twelve lead electrocardiograms recorded during the test included tracings with the patient standing and supine before exercise, at the end of each 3 minute stage, immediately after completion of the exercise test and 2, 4, 6, 10 and 20 minutes during the recovery period or until the ST segment deviation returned to baseline. The entire set of electrocardiograms from each patient was sent to a centralized ECG Core Laboratory, where all of the ST segment interpretations were performed by one cardiologist (P.H.S.). ST segment deviations were compared with the PQ isoelectric line, and were recorded with reference to the J point and 0.04 and 0.08 second after inscription of the J point.

After the 6 month visit, the health status of all patients was ascertained at 6 month intervals by telephone communication. The date of death was recorded for patients who died. Patients who developed a nonfatal recurrent infarction were identified, and the diagnosis was confirmed by review of the hospitalization records.

End points. Mortality, the development of nonfatal recurrent infarction and the need for coronary artery bypass surgery during the 12 months after the 6 month postinfarction visit were related to results of the exercise test to determine risk. Inability to perform the test for either cardiac or noncardiac reasons was evaluated as a potential prognostic variable. Patients taking a beta-adrenergic blocking agent at the time of the test were evaluated as a separate group, as were those taking digoxin or those with baseline features that could obscure the interpretation of the ST segment response to exercise, such as the presence of left ventricular hypertrophy on the rest electrocardiogram. The ST segment analysis was not performed in those patients with left or right bundle branch block.

Prognosis was also compared with the clinical assessment (history and physical examination) at the 6 month visit to determine the potentially independent power of information based on the exercise test.

Statistical analyses. Differences in the rates of mortality, recurrent nonfatal infarction and coronary artery bypass surgery were assessed using chi-square tests and Fisher's exact test where sample size was limited. Survival was evaluated further with life table techniques, with generalized Savage test statistics for those exercise test variables significantly associated with mortality. Student's t tests were used to test differences of means for variables of the continuous type.

Results

Clinical Characteristics

Among the 985 patients randomized to MILIS, 849 (86%) developed a myocardial infarction, confirmed by the Creatine Kinase Core Laboratory. Only those patients with a confirmed infarction were included in this study. At the time of the scheduled exercise test 6 months after infarction, 130 patients (15%) had died and 719 patients (85%) remained alive. Among the survivors, 473 (66%) performed the test and 246 patients (34%) did not. Among the 473 patients who performed the exercise test, the mean age was 54.8 years (range 20 to 75) and 374 patients (79%) were male. Ninety-four patients (20%) had had an infarction before their index infarction, and 11 patients (2%) had another infarction between the time of the index infarction and the time of the 6 month follow-up visit. The index infarction was transmural in 298 patients (63%), nontransmural in 133 patients (28%) and could not be identified on the surface electrocardiogram (because of the presence of bundle branch block, for example) in 42 patients (9%).

Among the 246 patients who did not perform the exercise test, the reasons for not performing the test included lack of consent (113 patients, 46%), cardiac limitations (68 patients, 28%), noncardiac physical limitations (46 patients, 19%) and other miscellaneous reasons (19 patients, 8%).

Among the 473 patients who performed the test, 122 patients (26%) had taken digoxin in the preceding 24 hours and 185 patients (39%) had taken a beta-adrenergic blocking agent in the same interval. Fifteen patients (3%) exhibited left ventricular hypertrophy and 24 (5%) exhibited left or right bundle branch block on the rest electrocardiogram.

Exercise Test Performance

No complications resulted from the exercise test. Exercise was terminated for the reasons outlined in Table 1. The test performance characteristics and their prognostic significance are shown in Table 2. Ninety patients (20%) developed angina during the exercise, and in 44 (10%) of the patients, the angina was accompanied by ST segment depression of 1 mm or greater. One hundred twenty-four patients (28%) developed horizontal or downsloping ST segment depression of 1 mm or greater. Exertional ST segment elevation of 1 mm or greater occurred in 74 patients (17%), of whom all but 2 exhibited a Q wave in the same or adjacent lead on the rest electrocardiogram. During the test, 73 patients (15%) manifested an "inadequate blood pressure response," defined as an increase in systolic blood pressure of less than 10 mm Hg from rest to peak exercise. A decrease in systolic arterial pressure of 10 mm Hg or more during exercise occurred in 22 patients (5%). Ventricular premature depolarizations developed during exercise in 130 patients (27%), and 48 of these patients developed frequent ventricular premature depolarizations (> 6/min). One hundred seventy patients (36%) were unable to complete stage I (5 METS) of the modified Bruce protocol.

Clinical Outcome

In the year after performance of the exercise test (that is, 6 to 18 months after infarction) 13 (3%) of the 473 patients died, 20 (5%) of the 440 patients who performed the test and who had detailed follow-up data available developed a nonfatal recurrent infarction and 9 patients (2%) underwent coronary artery bypass surgery. This low risk group is in contrast to the 68 patients who could not perform the test because of cardiac limitations. Among the latter patients, 11 (16%) died, and 8 (14%) of 59 developed a nonfatal recurrent infarction (both differences $p < 0.05$ compared with those who performed the test). Two patients (3%) underwent coronary bypass surgery. Thus, the overall results in the patients who did not perform the test because of cardiac limitations were worse than those in the patients who performed the test.

Among the 178 patients who did not perform the test because of lack of consent, noncardiac physical limitations or other miscellaneous reasons, 7 patients (4%) died, 12 (8%) of 151 patients developed a nonfatal recurrent infarction and 2 patients (1%) underwent coronary bypass surgery.

Table 1. Reasons for Terminating Exercise Test in 473 Patients

Reason	n	(%)*
Fatigue	296	(63)
Shortness of breath	141	(30)
Angina	67	(14)
Claudication	28	(6)
Lightheadedness	16	(3)
Decrease in systolic BP ≥ 10 mm Hg	14	(3)
Ventricular tachycardia or >25% beats were VPDs	6	(1)
Peripheral circulatory insufficiency	7	(1)
Target heart rate achieved	15	(3)
Other	35	(7)

*Total exceeds 100% because some patients discontinued exercise for more than one reason. BP = blood pressure; VPDs = ventricular premature depolarizations.

Table 2. Prediction of Mortality and Nonfatal Myocardial Infarction in the Year After the Exercise Test 6 Months After Index Infarction

	Death (n = 24)	Recurrent Nonfatal MI§ (n = 28)
Cardiac inability to perform exercise test		
Yes (n = 68)	16%†	14%*
No (n = 473)‡	3%	5%
Test performance variable in those who performed test	(n = 13)	(n = 20)
Angina and/or ST depression ≥ 1 mm		
Angina alone (n = 46)	2%	0%
ST depression alone (n = 80)	1%	1%
Angina and ST depression (n = 44)	2%	5%
No angina or ST depression (n = 278)	3%	6%
ST depression ≥ 1 mm		
Yes (n = 124)	2%	3%
No (n = 324)	3%	5%
ST elevation ≥ 1 mm		
Yes (n = 74)	8%†	4%
No (n = 374)	2%	4%
Inadequate BP response		
Yes (n = 73)	10%†	6%
No (n = 399)	2%	4%
Decrease ≥ 10 mm Hg in systolic BP during exercise		
Yes (n = 22)	9%	5%
No (n = 451)	2%	5%
Exertional VPDs		
Yes (n = 130)	6%†	4%
No (n = 343)	1%	5%
Inability to exercise beyond stage I		
Yes (n = 170)	6%†	2%*
No (n = 303)	1%	6%
ST abnormal > 6 min of recovery		
Yes (n = 77)	5%	7%
No (n = 372)	2%	4%

*$p < 0.05$; †$p < 0.01$; ‡Some of the exercise test measurements could not be obtained from all 473 patients; §Sample size was 440 of 473 for nonfatal recurrent myocardial infarction with adequate follow-up information. MI = myocardial infarction; other abbreviations as in Table 1. Values in parentheses are numbers of patients.

Thus, the overall results in this group were similar to those in the patients who performed the test (p = NS).

Prognostic Value of Exercise Test Performance

Mortality (Table 2, Fig. 1). Mortality after 1 year in patients unable to perform the treadmill test 6 months after infarction because of cardiac limitations was significantly higher than that in patients who performed the test (16 versus 3%, $p < 0.01$). Among patients who performed the test, those who developed exercise-induced ST segment elevation had a higher 1 year mortality rate than that of patients who did not (8 versus 2%, $p < 0.01$) (Fig. 2). Failure to increase systolic arterial pressure during the test was also associated with a significantly higher mortality rate than that in those who did raise arterial pressure (10 versus 2%, $p < 0.01$) (Fig. 2). The poor prognosis associated with an inadequate blood pressure response was most marked in patients who were not taking a beta-adrenergic blocking agent at the time of the test (18 versus 2% mortality rate, $p < 0.01$). Development of any ventricular premature depolarizations during exercise was associated with an increased mortality rate (6 versus 1%, $p < 0.01$) (Fig. 2). Frequent ventricular premature depolarizations (> 6/min) were associated with a higher mortality rate than that in patients without this finding (8 versus 2%, $p < 0.04$).

Limited exercise capacity was associated with an increased risk of death in the subsequent year. Mean exercise duration (± standard error) among the 13 patients who died was 7.34 ± 0.96 versus 10.62 ± 0.19 minutes for the 460 survivors ($p < 0.01$). Similarly, patients unable to exercise beyond stage I of the modified Bruce protocol had a significantly higher mortality rate than that of those able to exercise to stage II (6 versus 1%, $p < 0.01$) (Fig. 2).

Mortality assessment based on a combination of exercise test variables. Categories of risk for mortality based on combinations of individual prognostic variables identified in this study (Table 2) are shown in Figure 1, with equal weight assigned to each of the four high risk features: in-

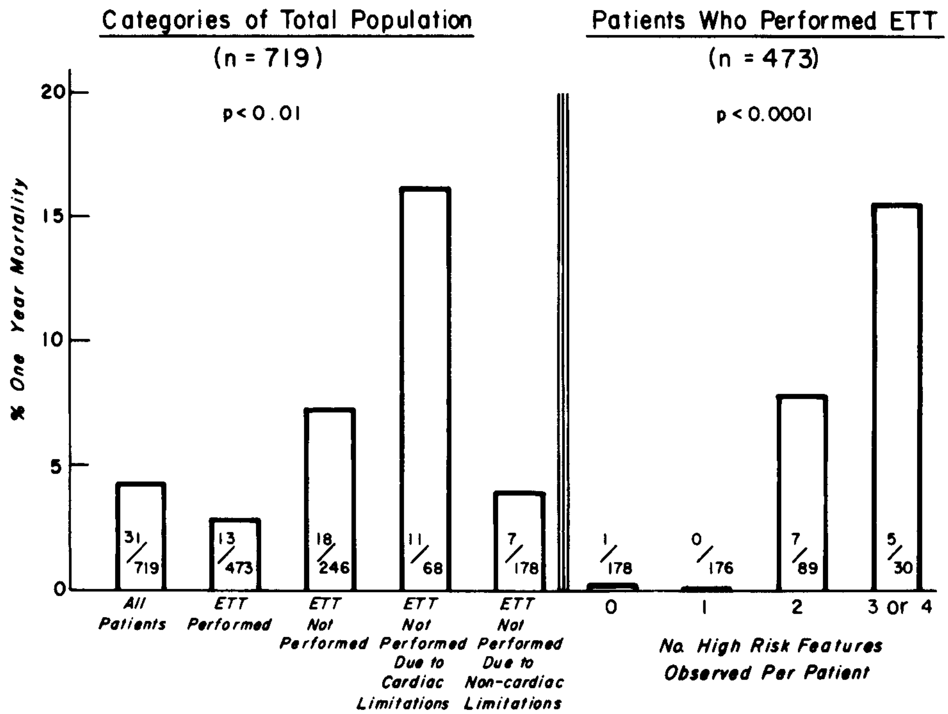

Figure 1. One year death rate after health visit 6 months after myocardial infarction. For patients who performed the treadmill exercise test (ETT), death rate is based on consideration of the number of high risk features observed. The high risk features considered were an inadequate systolic blood pressure response, inability to exercise beyond stage I of the modified Bruce protocol, development of any ventricular premature depolarizations or exertional ST segment elevation during the test. The denominator for each *bar* indicates the number of patients manifesting the number of high risk features observed. The numerator indicates the number of patients in the group who died. Of the 473 patients who performed the test, 447 were capable of exhibiting each of the four high risk features, and 26 were capable of exhibiting only three high risk features. Twenty-five patients were excluded from the ST segment analysis because of an uninterpretable ST segment (24 with left or right bundle branch block and 1 with technical failure of the electrocardiograph) and 1 patient could not have his blood pressure determined during exercise or in the recovery period.

adequate systolic blood pressure response, inability to exercise beyond stage I of the modified Bruce protocol, development of any ventricular premature depolarizations or exertional ST segment elevation of 1 mm or greater during the test. The incidence rate of death in the year after the test was only 1% among the 178 patients who manifested none of the four high risk performance features, but increased to 17% in the 30 patients who manifested three or four high risk features. (The number of patients (n = 3) who exhibited all four risk features was too small to allow statistical analysis and these patients have therefore been included with the group of patients who exhibited three risk features.) The 68 patients who were unable to perform the treadmill test because of cardiac limitations manifested a 1 year mortality rate (16%) as high as that of the highest risk stratum of patients who performed the test (Fig. 1), while the 178 patients who did not perform the test for reasons other than cardiac limitations had a mortality rate of only 4%.

Recurrent nonfatal myocardial infarction (Table 2). Of the total of 650 patients, 40 (6%) developed a nonfatal recurrent infarction 6 to 18 months after the index infarction. This group included 20 (5%) of 440 patients who performed the test and 20 (10%) of 210 patients who did not. Among the latter, recurrent nonfatal infarction occurred in 8 (14%) of 59 patients who did not perform the test because of cardiac disability and in 12 (8%) of 151 patients who did not perform the test for noncardiac reasons (p = NS). Thus, the incidence of recurrent nonfatal infarction was significantly higher among those patients who were unable to perform the exercise test because of cardiac limitations (14%) compared with that among those who performed the test (5%) ($p < 0.05$).

Coronary artery bypass surgery. Among the 440 patients who performed the test, 9 (2%) underwent coronary bypass surgery in the subsequent year. The only exercise test variable associated with bypass surgery was the development of ST segment depression of 1 mm or greater during the test. Six (5%) of the 116 patients with exertional ST segment depression underwent bypass surgery compared with 2 (1%) of 301 patients who did not exhibit that variable ($p < 0.01$). Coronary surgery was performed in 2 (3%) of 59 patients who did not perform the test because of cardiac limitations and in 2 (1%) of 151 patients who did not perform the test for noncardiac reasons (p = NS compared with the patients who performed the test).

Effect of beta-blocking agent or digoxin use or rest electrocardiographic abnormality at the time of the exercise test. There was no consistent difference in the predictive value of the test performance features when the re-

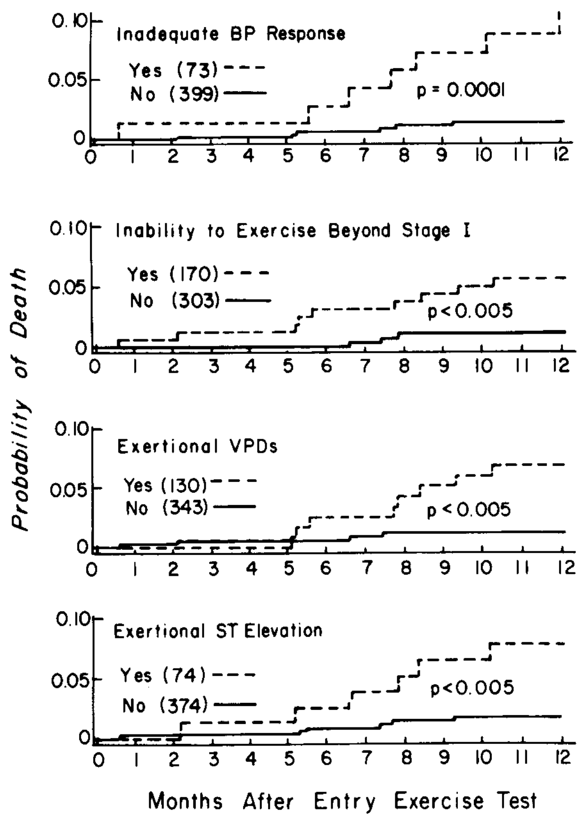

Figure 2. Cumulative probability of death in the 12 months after the exercise test performed 6 months after infarction on the basis of the observation of an inadequate systolic blood pressure (BP) response, inability to exercise beyond Stage I of the modified Bruce protocol, the development of ventricular premature depolarizations (VPDs) or exertional ST segment elevation. The number of patients for the variable "inadequate blood pressure response" is 472 because blood pressure could not be determined in one patient. The number of patients for the variable "exertional ST elevation" is 448 because the ST segment could not be interpreted in 25 patients (24 with left or right bundle branch block and 1 with technical failure of the electrocardiograph).

sults were analyzed separately on the basis of use of beta-adrenergic blocking agents, although only one patient died in the beta-blocker group. There was no difference in the predictive value of the ST segment response in the subgroup of patients not taking digoxin at the time of the test or in those patients with left ventricular hypertrophy.

Prognostic Value of Clinical Versus Exercise Test Performance Characteristics

To determine whether exercise test performance variables provided prognostic insights beyond those obtained from clinical characteristics alone, we examined the prognostic significance of the features from the history and physical examination obtained at the time of the test 6 months after infarction to predict the subsequent 1 year mortality (Table 3). The MILIS study group was analyzed first on the basis of all patients available at 6 months after infarction (n = 698) to determine the prognostic value of the clinical characteristics alone. Then the subgroup of patients who were well enough and consented to perform the treadmill test (n = 473) was analyzed to determine whether these clinical features remained predictive of mortality in patients who performed the test and whether the test provided prognostic insight not available from clinical evaluation.

Prognostic value of heart failure and angina. Among the entire group alive 6 months after infarction, the presence of either heart failure or angina at the 6 month visit was strongly associated with mortality in the subsequent 12 months. Of the 93 patients with a history of heart failure at 6 months, 14% died in the next 12 months, while only 3% of the 582 patients without heart failure died ($p < 0.01$). Similarly, 8% of the 235 patients with angina at 6 months died in the subsequent year, compared with only 3% of the 411 patients without angina ($p < 0.01$). As might be anticipated, the combined presence of angina and heart failure

Table 3. Comparison of Prognostic Significance of Clinical Features in All Patients Versus Those Who Performed an Exercise Test

Clinical Feature Noted at 6 Month Visit	Mortality Among All MI Patients (n = 698)	Mortality Among MI Patients Who Performed Exercise Test (n = 473)
History of congestive heart failure		
Yes	13/93 (14%)	0/32 (0%)
No	20/582 (3%)†	13/429 (3%)
History of angina		
Yes	18/235 (8%)	4/143 (3%)
No	12/411 (3%)†	8/290 (3%)
History of MI in addition to index MI		
Yes	16/168 (10%)	5/103 (5%)
No	18/530 (3%)†	8/370 (2%)
Abnormal neck vein distension		
Yes	1/13 (8%)	0/5 (0%)
No	30/591 (5%)	13/461 (3%)
Pulmonary rales		
Yes	9/43 (21%)	1/16 (6%)
No	22/563 (4%)†	12/451 (3%)
Presence of S_3		
Yes	4/31 (13%)	0/14 (0%)
No	27/545 (5%)	13/429 (3%)
Cardiomegaly on chest X-ray		
Yes	9/51 (18%)	1/29 (3%)
No	8/117 (7%)*	5/91 (5%)

*$p < 0.05$; †$p < 0.01$. MI = myocardial infarction; S_3 = third heart sound.

was a particularly poor prognostic sign. Nine (16%) of 58 patients with both conditions died, while the absence of both conditions was associated with a low mortality (10 [3%] of 373 patients). Other manifestations of heart failure, such as the presence of pulmonary rales on physical examination and cardiomegaly on chest X-ray study, were also powerful predictors of mortality in this group of patients after infarction (21% of 43 patients with rales and 18% of 51 patients with cardiomegaly at the 6 month visit died in the next year, compared with only 4% of the 563 without rales and only 7% of the 117 patients without cardiomegaly).

Clinical features versus ability to perform the exercise test. Among the subgroup of patients who performed the treadmill test 6 months after infarction, none of the clinical features predicted mortality in the following year. In this subgroup, none of the 32 patients who had heart failure at 6 months died compared with 3% of the 429 patients who did not have heart failure (p = NS). Similarly, in this subgroup of patients 3% of the 143 patients with angina at 6 months died as did 3% of the 290 patients without angina (p = NS). Therefore, these clinical characteristics were discriminatory only among the 205 patients who did *not* perform the treadmill test. Among these, the mortality rate was 2% (2 of 99 patients) in those without angina or heart failure, 10% (5 of 50 patients) among those with angina but not heart failure, 12% (2 of 17 patients) among those with heart failure without angina and 23% (9 of 39 patients) among those with both angina and heart failure. These differences were also striking among the 63 patients who did not perform the test because of cardiac disability. In this group, the mortality rate was 8% (1 of 12 patients) among those without angina or heart failure, 5% (1 of 20 patients) among those with angina but not heart failure, 14% (1 of 7 patients) among those with heart failure but not angina and 29% (7 of 24 patients) among those with both angina and heart failure.

Hence, among all 6 month survirors of infarction, clinical characteristics identified those at risk of death in the subsequent 12 months. Among the low risk patients who were well enough and consented to perform an exercise test 6 months after infarction, however, the exercise performance characteristics were much more powerful in estimating prognosis than were clinical features obtained at the same time in the convalescent phase.

Discussion

Use of exercise test after myocardial infarction. The submaximal exercise test performed in the early convalescent phase (1 to 3 weeks) after an uncomplicated myocardial infarction has been shown to be a safe and useful tool for assessing prognosis (3–14,16,18,19–22,31). Combining the submaximal exercise test with exercise radionuclide ventriculography or thallium-201 scintigraphy has proved even more useful in predicting prognosis in the 6 months after infarction (32–34). Because left ventricular function improves gradually and then stabilizes over the ensuing months (35) as the infarcted myocardium heals (36,37), a second treadmill test is often performed 6 to 8 weeks after infarction, using a maximal exercise protocol, to stress the cardiovascular system to its limits and thereby derive more prognostic information (4,5,10,21,22). Exercise tolerance increases progressively over at least 3 months (4,21), as does maximally tolerated myocardial oxygen demand, as reflected by systolic blood pressure and rate-pressure (double) product. Although ischemic ST segment responses and ventricular ectopic activity occur with comparable frequency between 3 and 11 weeks after infarction (4,21), a maximal exercise test performed 2 to 3 months after the acute event elicits abnormal responses more often, and, therefore, more prognostic information, than does the submaximal treadmill test 1 to 3 weeks after infarction (22,30).

Prediction of mortality, recurrent nonfatal infarction and coronary bypass surgery using the exercise test 6 months after infarction. There is limited experience concerning the value of a maximal exercise test performed 6 months after myocardial infarction in predicting subsequent morbidity and mortality. There have been many studies in patients with previous infarction, however, that suggest that the exercise test can identify the presence of multivessel disease and poor left ventricular function, which are the underlying determinants of subsequent morbidity and mortality (38–42). The current study provides information on a large group of patients who were observed prospectively for 1 year after the 6 month postinfarction clinical evaluation and exercise test. Our results indicate that the mortality during the year after a 6 month exercise test is significantly increased in patients who exhibit any of the following: inability to perform the test because of cardiac limitations, ST segment elevation of 1 mm or greater, an inadequate blood pressure response during exercise, development of any ventricular premature depolarizations during exercise or the recovery period or inability to exercise beyond stage I of the modified Bruce protocol. By utilizing a combination of these high risk prognostic features, one can stratify patients in terms of risk of mortality. Patients who exhibited none of the high risk features had a 1 year mortality rate of only 1%, whereas patients who demonstrated more than one characteristic experienced a mortality rate as high as 17% (Fig. 1).

Results of most studies have shown that development of ST segment depression during an exercise test performed early in convalescence is associated with increased mortality (3–11), although conclusions are not consistent (16,19,20). Other variables such as exercise duration (13–16), inadequate blood pressure increase with exercise (16–18), development of angina (16,19), ST segment elevation (12), ventricular ectopic activity (16) or inability to perform the test because of cardiac limitations (10,16,18) may be more powerful descriptors. Disparate conclusions may reflect differences in study design, sample size, exercise test procedures or length of follow-up. Our observations indicate that many of the exercise test performance characteristics that are predictive of mortality in the early phase after infarction remain predictive for those patients who survive to the later convalescent phase.

The prognostic power of the exercise performance variables observed in this study is underscored by the fact that these variables predicted mortality in a group of patients whose 1 year mortality rate was only 3%. The poor predictive value of exercise-induced angina or ST segment depression observed in this study may be due to the exclusion of patients in whom myocardial ischemia is readily provoked, such as those with angina that occur more than once daily or severely limits activities. Among patients who performed the test, the development of ST segment depression predicted those who subsequently underwent a coronary bypass procedure, and it is possible that identification of these patients with jeopardized myocardium led to the surgical or pharmacologic intervention that altered their prognosis, thereby diluting the significance of that test variable. However, because only 6 (5%) of the 116 patients who exhibited ST segment depression underwent bypass surgery, it is unlikely that the altered course of these few patients exerted a major impact on the prognostic significance of the ST segment depression variable. In fact, the exercise performance features predictive of mortality in this study are those most frequently associated with abnormal left ventricular wall motion and impaired global function, namely, exercise-induced ST segment elevation in the distribution of transmural infarction (43), inadequate blood pressure response to exercise and limited exercise tolerance. It is widely recognized that the presence of left ventricular dysfunction is an important marker for subsequent mortality (11,44). These findings are similar to those of Krone et al. (16), who found that cardiac mortality was best related to pulmonary congestion during the acute hospitalization and to a systolic blood pressure of less than 110 mm Hg, angina and ventricular couplets during a predischarge exercise test, whereas the need for coronary bypass surgery was best correlated with ischemic ST segment depression or angina during the test.

Recurrent nonfatal infarction was predicted only by inability to perform the treadmill test because of cardiac limitations. Recurrent episodes of infarction that could have been predicted from results of the submaximal exercise test performed 1 to 3 weeks after infarction may have already occurred by the time the 6 month test was performed (23,26,27). Thus, predischarge exercise test performance features predictive of recurrent infarction, such as the development of angina, ST segment depression, poor exercise capacity, blunted arterial pressure increase with exercise or the development of supraventricular ectopic depolarizations (8,16,20), may lose their predictive significance when the test is performed in the late convalescent period (≥ 6 months after infarction). Furthermore, the mechanism of recurrent nonfatal infarction in some patients may be attributable to thrombosis (45), which would not necessarily be predictable on the basis of exercise test results. Previous experience with treadmill testing in the late convalescent phase to predict nonfatal cardiac events is limited (5,9,46).

Survivors of uncomplicated infarction are often treated with a beta-adrenergic blocking agent (47–49). There were too few deaths in this selected population to allow for adequate assessment of the effect of beta-blocker use on the value of the treadmill test in the prediction of mortality in the subsequent year. Beta-blockers do not detract from the prognostic value of an exercise test performed in early convalescence (3,7).

Comparison of prognostic significance of clinical assessment and exercise test performance. Our results indicate that clinical assessment utilizing history, physical examination and chest X-ray study obtained 6 months after infarction provides important prognostic information for the total group of patients who survive infarction. However, among the low risk patients who were not severely limited by angina or heart failure and who were capable of performing an exercise test, these clinical variables were not predictive of mortality. The maximal exercise test therefore provides prognostic information not available from clinical assessment alone in patient groups from which high risk subjects have been excluded on clinical grounds. In the early convalescent phase (1 to 6 weeks after infarction), the submaximal exercise test has also been found to contribute independently used prognostic information (3,9,11,12,14,16), although some investigators (50) have observed that clinical assessment and ST segment depression on the predischarge rest electrocardiogram predict prognosis more accurately than do variables derived from the exercise test.

Clinical implications. Our results suggest that the exercise test performed 6 months after acute myocardial infarction provides prognostic information not available from clinical assessments alone. A submaximal exercise test performed before hospital discharge after myocardial infarction is standard practice. A maximal effort treadmill test 6 months after infarction may help to identify those survivors without clinical complications who remain at particularly high risk in the subsequent 12 months.

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Appendix
Multicenter Investigation of the Limitation of Infarct Size (MILIS) Study Personnel

Clinical Centers

Barnes Hospital, Washington University School of Medicine, St. Louis, MO. Allan S. Jaffe, MD, Principal Investigator; Robert Roberts, MD, Principal Investigator; Edward Geltman, MD, Co-Investigator; Dan Biello, MD, Nuclear Medicine Coordinator; Rosanne Wettach, RN, MNP, Research Nurse Coordinator; Ava Ysaguire, Susan Payne and Linda Wilson, Data Coordinators.

Massachusetts General Hospital, Boston, MA. Herman K. Gold, MD, Principal Investigator; Robert C. Leinbach, MD, Principal Investigator; Tsunehiro Yasuda, MD; Wendy Werner, RN and Mary McHugh, RN, Research Nurse Coordinators; Harry Garabedian, Data Coordinator.

Medical Center Hospital of Vermont, University of Vermont College of Medicine, Burlington, VT. Daniel S. Raabe, Jr., MD, Principal Investigator; Walter Gundel, MD; Marian Dornell, RN, Maureen Hawley, RN, Patricia Beecher, RN, Kathleen Cornell, RN, and Karen Helminger, RN, Research Nurse Coordinators; Raina Maynard, Data Coordinator.

Harvard Medical School/Brigham and Women's Hospital, Boston, MA. Eugene Braunwald, MD, Principal Investigator; Peter H. Stone, MD, Joseph S. Alpert, MD and Robert Rude, MD, Clinical Unit Directors; Nancy E. Taplin, RN, Kathryn Shea, RN, Debbie Shiner, RN, Research Nurse Coordinators.

Parkland Memorial Hospital, University of Texas Health Science Center at Dallas, TX. James T. Willerson, MD, Principal Investigator; Robert E. Rude, MD, Clinical Unit Director; Charles Croft, MD; Robert Dillon, MD; Kevin Wheelan, MD; Christopher Wolfe, MD; Barbara Moses, RN, Sandra Cochran, RN, Marvin Akers, RN, Joan Reinert Corey, RN, Vicki Gillespie, RN and Barbara Fitzpatrick, RN, Research Nurse Coordinators; Kris Kraft, Unit Clerk.

Creatine Kinase Core Laboratory

Washington University School of Medicine, St. Louis, MO. Burton E. Sobel, MD, Principal Investigator; Robert Roberts, MD, Principal Investigator; Allan Jaffe, MD; Cynthia Ritter, Laboratory Coordinator; Steven Mumm, Laboratory Technician.

Cardiovascular Pathology Core Laboratory

Duke University Medical Center, Durham, NC. Donald B. Hackel, MD, Principal Investigator; Raymond E. Ideker, MD, PhD; Keith A. Reimer, MD, PhD; Eileen Mikat, PhD.

Technetium-99m Pyrophosphate Myocardial Scintigram Core Laboratory

University of Texas Health Science Center at Dallas, Dallas, TX. James T. Willerson, MD, Principal Investigator; Samuel E. Lewis, MD, Laboratory Director; Robert W. Parkey, MD, Laboratory Co-Director; Irma Dobbins, Laboratory Coordinator.

Holter Recording Core Laboratory

Washington University School of Medicine, St. Louis, MO. Lewis J. Thomas, Jr., MD, Principal Investigator; Robert Roberts, MD, Co-Principal Investigator; Kenneth W. Clark, Laboratory Director; Kathleen Madden, Laboratory Coordinator; J. Phillip Miller, Biostatistician.

Radionuclide Ventriculogram Core Laboratory

Massachusetts General Hospital, Boston, MA. H. William Strauss, MD, Principal Investigator; Nathaniel M. Alpert, MD, Co-Principal Investigator; Kenneth A. McKusick, MD, Clinical Director, Nuclear Medicine Division; Tsunehiro Yasuda, MD; Karen Kelly, Laboratory Coordinator; Annali Kiers, Leander Blakeman and Merrill Griff, Laboratory Coordinators and Nuclear Medicine Technicians.

ECG Core Laboratory

Harvard Medical School/Brigham and Women's Hospital, Boston, MA. Eugene Braunwald, MD, Principal Investigator; Zoltan G. Turi, MD, Laboratory Director; John D. Rutherford, MD, Laboratory Director; James E. Muller, MD, Laboratory Co-Director; Peter H. Stone, MD, Laboratory Co-Director for ETT Analysis; Gail Z. Alymer, Susan G. Albert, PA; Jennifer Forage and Michael Miller, Laboratory Coordinators; Neil Rhodes, Matthew Levine, Jeremy Pool, and John Rees, Programmers/Analysts; Jane Soukup and David Mayberry, Computer Operators.

Data Coordinating Center

Research Triangle Institute, Research Triangle Park, NC. W. Kenneth Poole, PhD, Principal Investigator; Tyler D. Hartwell, PhD, Co-Principal Investigator; Corette Parker, MSPH, Project Coordinator, Biostatistician; Connie Hobbs, Norma Fox, MPH and Susan Warwick, RN, Data Coordinators; Priscilla Rigby, RN, Data Management Coordinator; Thomas S. Farrell and Debra Fleischman, Computer Programmers; Nancy Gustafson, MS, Susan K. Settergren, MS, B.J.G. York, MS, James H. Crowder, MPH, Carolyn Stuart, MSPH and Vicki Davis, MS, Statisticians; Lee Larsen, Statistical Clerk.

Clinical Coordinating Center

Harvard Medical School/Brigham and Women's Hospital, Boston, MA. Eugene Braunwald, MD, Principal Investigator; James E. Muller, MD; Zoltan G. Turi, MD; Ellenjane Scheiner, Project Coordinator; Norman R. Stein, Financial Administrator.

Program Office

Cardiac Diseases Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Bethesda, MD. Thomas Robertson, MD, Project Officer; Eugene R. Passamani, MD, Project Officer; Michael B. Mock, MD, Project Officer; Suzanne M. Mullin, RN, MPH, Clinical Trials Nurse Administrator; Roland Castle, Contracting Officer; Patrick M. Sullivan, Contract Officer; K. Gordan Lan, PhD, David DeMets, PhD and James Ware, PhD, Biostatisticians.

MILIS Policy Advisory Board

William L. Ashburn, MD; Eugene Braunwald, MD; Paul Canner, PhD; Robert L. Frye, MD (Chairman); Lawrence E. Hinkle, Jr., MD; Andrew Z. Keller, DMD; Paul Meier, PhD; Leroy Walters, PhD; Nanette Wenger, MD.

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