Exercise Treadmill Testing Is a Poor Predictor of Anatomic Restenosis After Angioplasty for Acute Myocardial Infarction

Michael B. Honan, MD, James R. Bengtson, MD, MPH,
David B. Pryor, MD, David S. Rendall, PA-C, Richard S. Stack, MD,
Tomoaki Hinohara, MD, Thomas N. Skelton, MD, Robert M. Califf, MD,
Mark A. Hlatky, MD, and Daniel B. Mark, MD, MPH

This study evaluated whether an exercise treadmill test could predict restenosis in 289 patients 6 months after a successful emergency angioplasty of the infarct-related artery for acute myocardial infarction. After excluding those with interim interventions (64), medical events (36), or medical contraindications to follow-up testing (25), both a treadmill test and a cardiac catheterization were completed in 144 patients, 88% of those eligible for this assessment. Four patients with left bundle branch block or pacemaker rhythm at the time of treadmill testing were also excluded from analysis. Of six follow-up clinical and treadmill variables examined by multivariable logistic regression analysis, only exercise ST deviation was independently correlated with restenosis at follow-up ($\chi^2=5$, $p=0.02$). The clinical diagnosis of angina at follow-up, although marginally related to restenosis when considered by itself ($p=0.04$), did not add significant information once ST deviation was known. The sensitivity of ST deviation of 0.10 mV or greater for detecting restenosis was only 24% (13 of 55 patients), and the specificity was 88% (75 of 85 patients). The sensitivity of exercise-induced ST deviation for detection of restenosis was not affected by extent or severity of wall motion abnormalities at follow-up, by the timing of thrombolytic therapy or of angioplasty, or by the presence of collateral blood flow at the time of acute angiography. A second multivariable analysis evaluating the association of the same variables with number of vessels with significant coronary disease at the 6-month catheterization found an association with both exercise ST deviation ($p=0.003$) and exercise duration ($p=0.04$). Angina symptoms and exercise treadmill test results in this population had limited value for predicting anatomic restenosis 6 months after emergency angioplasty for acute myocardial infarction. (Circulation 1989;80:1585-1594)

The value of early angioplasty in the treatment of acute myocardial infarction depends not only on its ability to establish reperfusion of the infarct-related artery but also on its ability to ensure continued patency of this vessel. Restenosis has occurred within the first 6–12 months in 25–50% of patients after elective coronary angioplasty\textsuperscript{1} and in 18–45% of patients after angioplasty performed in the setting of an evolving myocardial infarction.\textsuperscript{2} A noninvasive method of identifying restenosis might assist clinicians and researchers evaluating these patients.

Angioplasty performed shortly after myocardial infarction has been shown to decrease exercise-induced myocardial ischemia.\textsuperscript{3-5} Thus, restenosis in these patients might be manifested by an ischemic response to exercise. However, the role of exercise testing in detecting restenosis after angioplasty for acute myocardial infarction has not yet been explored. Because of its universal availability and relatively low cost, exercise electrocardiography is the functional test most commonly used by primary care physicians in postinfarct patient populations.\textsuperscript{6}
The purpose of our study was to determine whether anginal symptoms or exercise treadmill testing could detect angiographically defined restenosis 6 months after successful emergency coronary angioplasty in a consecutive series of acute myocardial infarction patients who were without interim events or contraindications to testing. Additionally, the relation of treadmill ST segment response to factors thought to be associated with greater myocardial salvage were examined in patients with restenosis.

Methods

Patient Population

We identified 321 consecutive patients in whom angioplasty of the infarct-related artery was attempted within 24 hours of onset of symptoms of acute myocardial infarction at Duke University Medical Center between April 1986 and April 1987 (Figure 1). Of these patients 289 (90%) with a successful procedure were prospectively enrolled in a follow-up protocol involving a repeat coronary angiogram and treadmill test 6 months later. Myocardial infarction was confirmed by elevation of creatinine kinase (CK)-MB isoenzymes to greater than 10 IU in all patients who survived the initial 24 hours of hospitalization.

PredischARGE events that disqualified patients from follow-up testing as part of this protocol included death (17), repeat angioplasty for reinfarction (19), repeat angioplasty for symptomatic restenosis without reinfarction (2), and coronary artery bypass surgery (9). Additionally, of the 242 remaining patients 173 (71%) underwent routine cardiac catheterization before discharge. This was followed by coronary bypass surgery in 13, elective coronary angioplasty in five, and detection of symptomatic restenosis in three and asymptomatic reclosure in six patients, each of which resulted in exclusion from the follow-up protocol. Fifteen additional patients in whom asymptomatic subtotal restenosis was detected without evidence of exercise-induced ischemia were not excluded because they would not have been detected in the absence of routine pre-discharge catheterization.

After discharge three patients who had reinfarction, seven who died, 14 who had coronary artery bypass surgery, and two who had interim elective angioplasty were also excluded. Twenty-five patients were considered by their physicians to have medical contraindications to either the catheterization or treadmill testing required by the protocol: 12 with unstable angina, three with renal insufficiency, three with multisystem disease, two amputees, one with paraplegia, one with previous cerebrovascular accident, one with a meningioma, and two for unclear reasons. These exclusions left 164 patients eligible for the follow-up protocol. Of these, 20 patients did not participate: 14 patients refused, three lived outside the southeastern United States, and three were lost to follow-up. Thus, 144 of the 164 (88%) eligible patients underwent follow-up coronary angiography and exercise testing at a median of 6.3 months (range, 2–11 months) after angioplasty and formed the study population.

Data Collection and Information System

The computerized medical information system used in this study has been described previously. Before both coronary angioplasty and follow-up catheterization, each patient received a directed cardiac history, physical examination, and resting 12-lead electrocardiogram. These data were entered prospectively in the computerized data base. Anginal symptoms at the follow-up visit were classified as absent or nonanginal, atypical, or typical.

Thrombolysis, Coronary Angioplasty, and Follow-up Coronary Angiography

Ninety percent of patients (129 of 144) received thrombolytic therapy before angioplasty, either as 1.5 million units streptokinase i.v. (103), as 150 mg recombinant tissue-type plasminogen activator (rt-PA) i.v. as part of the TAMI I protocol (14), or as variable doses of t-PA and urokinase intravenously as part of the TAMI II protocol (12).
Emergency angioplasty was performed, as described previously, on suitable individuals or sequential lesions with 75% or more residual stenosis of the infarct-related artery. Lesions in other vessels were not approached during the initial angioplasty. Patients enrolled in the TAMI I protocol were excluded from emergency angioplasty if they had suitable subtotal stenoses and were randomized to deferred angioplasty. The TAMI II protocol deferred patients from emergency angioplasty if they had subtotal occlusion without evidence of ongoing ischemia.

A successful angioplasty was defined as a reduction from a 75% or more initial luminal diameter stenosis to 50% or less residual stenosis as determined by a panel of at least two angiographers using an ordinal grading scale of 0%, less than 25%, 50%, 75%, 95%, and 100%, as previously described. Each patient was routinely treated before angioplasty with a 10,000-unit heparin bolus followed by a 500-1,000 unit/hr infusion for at least 24 hours. Patients were maintained on aspirin 325 mg/day, dipyridamole 75 mg three times a day, and a calcium channel blocker through the time of follow-up.

Follow-up left ventriculography and selective coronary arteriography were performed with multiple left anterior oblique and right anterior oblique views to determine whether restenosis had occurred and to establish the number of major coronary vessels with 75% or more stenosis. Restenosis was defined as recurrence of 75% or more luminal diameter stenosis at a site related to the angioplasty or to any angioplasty site if multiple lesions were dilated. Regional left ventricular wall motion analysis was performed with the centerline method, as described by Sheehan. Wall motion was assessed along 100 chords perpendicular to and equally spaced along a centerline created midway between traced end-diastolic and end-systolic right anterior oblique ventriculographic images and normalized by end-diastolic perimeter. The normal reference data base was composed of a population of 100 patients evaluated at Duke University who had no visible coronary stenosis, congenital or valvular heart disease, history of Prinzmetal’s angina, sudden death, previous myocardial infarction, cardiac surgery, coronary angioplasty, electrocardiographic abnormalities, major wall motion abnormalities, or ejection fraction less than 55%. The severity of hypokinesis in the infarct zone (SD/chord units) was calculated as the mean motion of chords lying in the 50% of the predefined infarct artery territory whose motion was most depressed compared with normal motion. The circumferential extent of hypokinesis was calculated as the set of contiguous chords in the infarct artery territory with wall motion more depressed than 1 SD below the normal mean and expressed as a percentage of the endocardial contour length.

**Exercise Testing**

Treadmill tests were performed just before follow-up cardiac catheterization using the Bruce protocol. Exercise was continued until the target heart rate was achieved or until development of limiting symptoms (angina, dyspnea, fatigue, or claudication), abnormalities of rhythm (ventricular tachycardia or frequent couplets) or blood pressure, or marked and progressive ST displacement (0.20 mV or more in the presence of typical angina or in the first stage of exercise). Any ST segment displacement (depression or elevation) registering 0.10 mV or more than the value at baseline that occurred during or after exercise and that was horizontal or sloping away from the baseline 0.08 seconds after the J point in three consecutive beats was measured to the nearest 0.05 mV with a calibrated grid. Measurement was made from the level of the PR segment if the resting ST segment was isoelectric or was displaced in the opposite direction from the exercise-induced changes; otherwise, measurement was made from the resting ST segment level. Exercise-induced ST deviation was defined as the largest net ST displacement in any of the 12 standard leads except ST elevation that occurred in leads with pathologic Q waves. The test was interpreted as positive if ST deviation was 0.10 mV or more, as negative adequate if less than 0.10 mV of ST deviation occurred and 85% of maximal predicted heart rate was achieved, as negative inadequate if ST deviation was less than 0.10 mV and maximal heart rate was less than 85% of predicted, and as indeterminate if the only exercise-induced ST deviation was elevation in leads with pathologic Q waves. Patients with left bundle branch block or paced rhythm had uninterpretable treadmill exercise responses and were not considered in the analysis. A previously developed treadmill angina index was assigned a value of 0 if angina was absent, 1 if typical angina occurred, and 2 if angina was the reason the patient stopped exercising. A taper of β-adrenergic blocking drugs over the week before return was designed to be completed six half-lives before treadmill testing.

**Data Analysis**

Continuous variables were summarized with medians and quartile ranges (25th to 75th percentile) while discrete variables were presented as number and percent of total group. The relation between restenosis and six follow-up clinical and treadmill variables was assessed with a stepwise multivariable logistic regression model. In a second analysis the same variables were incorporated into an ordinal logistic regression model to assess their predictive value in estimating the number of major coronary vessels (0, 1, 2, or 3) significantly diseased at follow-up cardiac catheterization. The variables assessed were treadmill interpretation (positive or
TABLE 1. Baseline Clinical and Catheterization Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Restenosis (58 patients) (n) (%)</th>
<th>No restenosis (86 patients) (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48/55/63</td>
<td>45/56/63</td>
</tr>
<tr>
<td>Male gender</td>
<td>50 (86)</td>
<td>75 (87)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39 (67)</td>
<td>53 (62)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (9)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>45 (78)</td>
<td>69 (80)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (7)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Infarct location by electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>18 (31)</td>
<td>33 (38)</td>
</tr>
<tr>
<td>Inferior, posterior</td>
<td>39 (67)</td>
<td>50 (60)</td>
</tr>
<tr>
<td>Lateral</td>
<td>1 (2)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Unclear (left bundle branch block)</td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Diseased vessels †</td>
<td>One</td>
<td>27 (47)</td>
</tr>
<tr>
<td></td>
<td>Two</td>
<td>21 (36)</td>
</tr>
<tr>
<td></td>
<td>Three</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>39/47/52</td>
<td>40/46/55</td>
</tr>
<tr>
<td>Time to arrival in catheterization lab (hr)</td>
<td>3.2/4.5/6.7</td>
<td>3.2/4.3/6.1</td>
</tr>
</tbody>
</table>

*Data presented as 25th/50th/75th percentile.
†p<0.05 by univariable analysis.

not positive), the magnitude of exercise-induced ST deviation (mV), maximal heart rate achieved on the treadmill, exercise duration (seconds), angina at follow-up, and treadmill angina index. Imbalances in baseline characteristics between groups with and without restenosis were also assessed in an exploratory fashion using univariable and multivariable logistic regression. To ensure that follow-up symptoms and treadmill test results continued to have independent predictive value beyond what could have been predicted from knowledge of baseline characteristics alone, the symptoms and treadmill test results of significant predictive value were reassessed after accounting for imbalances in baseline characteristics by incorporating these characteristics into the logistic regression models. The use of variables shown to be of value in predicting restenosis was illustrated by calculating their sensitivity, specificity, and positive and negative predictive values.20

Additionally, many factors previously associated with salvage of myocardium were examined in patients with restenosis to determine their effect on the exercise ST response. Among restenosis patients who were occluded at the time of initial angiography, treadmill positivity was evaluated for relation to 1) the presence of collaterals21–23 by the Fisher’s exact test and 2) time from symptom onset to catheterization and angioplasty21,22,24,25 by the Wilcoxon two-sample test. Among restenosis patients who were reperfused at the time of catheterization after prior thrombolytic therapy, the relation between treadmill positivity and time to treatment21,22,24,25 was assessed using the Wilcoxon two-sample test. Because extent and severity of hypokinesis have been correlated with infarct size,16,26 they were evaluated as potential measures of residual viable myocardium. Among patients with restenosis, the association of each of these measures of hypokinesis at follow-up catheterization with inability to manifest a positive treadmill test response was assessed by the Wilcoxon two-sample test.

Results

Restenosis and Baseline Characteristics

Of the 144 study patients 58 (40%) had restenosis, 27 (19%) had other significant coronary lesions, and 59 (41%) had no significant lesions at follow-up angiography. As shown in Table 1, most baseline clinical and catheterization characteristics, including age, gender, risk factors for coronary disease, infarct location, ejection fraction, and time to arrival in the catheterization laboratory, were similarly distributed between the patients with and without restenosis. Restenosis was associated with a greater number of diseased coronary vessels at the time of the initial catheterization (p=0.03).

Table 2 details the interventions undertaken during the early course of acute infarction. Restenosis occurred in 10 of 15 patients (67%) who received no thrombolytic therapy, in seven of 12 (58%) of those who received t-PA and urokinase, in six of 14 (43%) of patients who received t-PA alone, and in 35 of
103 (34%) of those who received streptokinase. Only one patient underwent two-vessel angioplasty acutely because of uncertainty about which was the infarct vessel. Multiple lesions were dilated in the infarct-related vessel in 28 of 144 patients (19%). Coronary dissection was visualized after 34% of the procedures. In univariate analysis the use of a thrombolytic agent other than streptokinase (p=0.05), presence of a total occlusion before angioplasty (p<0.001), and right coronary artery angioplasty (p=0.02) were associated with restenosis. Of all the characteristics displayed in Tables 1 and 2, only the presence of a baseline total occlusion (p<0.001) and angioplasty of the right coronary artery (p=0.03) were independently correlated with restenosis by multivariable logistic regression.

### Angina Symptoms and Treadmill Test Results at Follow-up

At a median of 6.3 months after the initial angioplasty, 51 of the 144 study patients (35%) had symptoms believed to represent angina. Of the 144 patients who underwent follow-up treadmill testing and coronary arteriography, four (3%) had uninterpretable results due to the presence of a left bundle branch block in three and a paced rhythm in one; they were excluded from logistic regression analysis. Among the remaining 140 patients, 23 patients (16%) had a positive test, 70 patients (50%) had a negative test after achieving target heart rate, 39 (28%) had a negative inadequate test, and eight patients (6%) had indeterminate results with no ST deviation other than ST elevation in leads with pathologic Q waves. Angina occurred during treadmill testing in only 18 patients (12%). By univariable analysis exercise-induced ST deviation (p=0.02) and angina at follow-up (p=0.04) were significantly associated with the presence of restenosis while maximum heart rate achieved, exercise duration, test interpretation, and the treadmill angina index were not (Table 3). By multivariable logistic regression analysis only the magnitude of exercise ST deviation remained significantly associated with the presence of restenosis (χ^2=5, p=0.02). The presence or absence of angina at the time of follow-up added no significant additional information. ST deviation remained predictive of restenosis even after accounting for imbalances in

<table>
<thead>
<tr>
<th>Table 3. Angina Symptoms and Treadmill Test Results at Follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Months to follow-up</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Angina symptoms†</td>
</tr>
<tr>
<td>None or nonanginal</td>
</tr>
<tr>
<td>Typical angina</td>
</tr>
<tr>
<td>Atypical angina</td>
</tr>
<tr>
<td>Maximum heart rate</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Test interpretation</td>
</tr>
<tr>
<td>Negative adequate</td>
</tr>
<tr>
<td>Negative inadequate</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Indeterminate (ST elevation in leads with pathologic Q waves)</td>
</tr>
<tr>
<td>Uninterpretable (LBBB, paced rhythm)‡</td>
</tr>
<tr>
<td>Exercise ST deviation (mV)†‡</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.10–0.15</td>
</tr>
<tr>
<td>0.16–0.20</td>
</tr>
<tr>
<td>≥0.21</td>
</tr>
<tr>
<td>Treadmill angina</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td>Nonlimiting</td>
</tr>
<tr>
<td>As a reason for stopping exercise</td>
</tr>
</tbody>
</table>

*Data are displayed as no. and percent of row or as 25th/50th/75th percentile.
†p<0.05 by univariable analysis.
‡Patients with uninterpretable results were excluded from the final analysis group.
LBBB, left bundle branch block.
the distribution of total occlusion of the infarct artery before angioplasty and of right coronary angioplasty.

The sensitivity of ST deviation of 0.10 mV or more for detecting restenosis was only 24% (Table 4), while the specificity of ST deviation less than 0.10 mV was 88%. The predictive value of a positive test was 57%, and that of a nonpositive test was 64%. The positive predictive value was improved among the 10 patients with more than 0.15 mV ST deviation (70%) and among the three patients with more than 0.20 mV ST deviation (100%).

Data on the presence of significant coronary disease in vessels other than the angioplasty vessel are shown in Table 3. A univariable analysis examining the association of follow-up angina and the five main treadmill variables with the number of major coronary vessels with significant stenoses at follow-up found exercise-induced ST deviation (p=0.003) and a positive exercise treadmill response (p=0.02) to be associated. An association with exercise duration was marginally significant (p=0.06). In the multivariable analysis exercise ST deviation was again the major predictor of number of diseased vessels (p=0.003), while exercise duration remained marginally significant (p=0.04).

**Predischarge Exercise Tests**

Although a predischarge treadmill test was not a part of the routine protocol for follow-up of these patients, many of the patients' personal physicians requested one. A Bruce protocol exercise test to 85% of maximal predicted heart rate was attempted in 73 of the 144 patients in the study group and a more limited test in five additional patients at a median of seven days postinfarct (range, 5–14 days). Only 12 of the 78 patients (15%) achieved 85% of predicted maximal heart rate. Only three predischarge tests (4%) were positive, while six (8%) were negative after achieving an adequate heart rate, 44 (56%) were negative inadequate, and 22 (28%) were indeterminate because the only ST deviation was ST elevation in leads with resting Q waves. Three tests (4%) were uninterpretable because of left bundle branch block or paced rhythm. All three patients with a positive treadmill test underwent predischarge coronary arteriography without evidence of restenosis or other significant coronary disease; none of the three had restenosis at 6-month angiography, and treadmill tests were negative adequate in all three patients at follow-up. Of the 58 patients who had restenosis at follow-up, 29 had undergone predischarge testing. Tests were positive in none, negative adequate in two, negative inadequate in 16, indeterminate in 10, and uninterpretable in one. Six of these 29 restenosis patients had a positive test at the time of follow-up, as did five of the 54 patients without restenosis whose initial exercise test was not positive. Thus, the follow-up treadmill test performance was similar among patients who had undergone predischarge testing (sensitivity, 21%; specificity, 91%) and in the entire follow-up population (sensitivity, 24%; specificity, 88%). Six additional patients who would have been candidates for the late follow-up protocol were excluded because a positive predischarge exercise test led to interim revascularization: two with positive treadmill tests underwent angioplasty, and four with ischemic responses to radionuclide angioiography underwent coronary artery bypass surgery.

**Table 4. ST Deviation 0.10 mV or More and Prediction of Restenosis**

<table>
<thead>
<tr>
<th>ST</th>
<th>Total</th>
<th>Deviation (mV)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>75</td>
<td>0</td>
<td>117</td>
</tr>
<tr>
<td>Present</td>
<td>42</td>
<td>≥0.10</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>55</td>
<td>140</td>
</tr>
</tbody>
</table>

Sensitivity, 13 of 55 or 24%; specificity, 75 of 85 or 88%; positive predictive value, 13 of 23 or 57%; negative predictive value, 75 of 117 or 64%.

**Table 5. Association of Treadmill Test Results With Evidence of Myocardial Salvage Among 55 Patients With Restenosis***

<table>
<thead>
<tr>
<th>Treadmill test result</th>
<th>Positive (n=13)</th>
<th>Nonpositive (n=42)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion state before angioplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occluded (n)</td>
<td>8</td>
<td>26</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Percent (n) with collaterals present</td>
<td>12 (1)</td>
<td>12 (3)</td>
<td></td>
</tr>
<tr>
<td>Time to catheterization (hr)</td>
<td>3.0/4.5/5.7</td>
<td>3.8/4.9/8.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Reperfused after thrombolytic (n)</td>
<td>5</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Time to administration (hr)</td>
<td>3.1/3.6/4.2</td>
<td>1.8/2.4/3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Reperfused without thrombolytic (n)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Regional wall motion at follow-up catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of hypokinesis (n chords)</td>
<td>22/27/57</td>
<td>13/31/55</td>
<td>0.92</td>
</tr>
<tr>
<td>Severity of hypokinesis (SD/chord)</td>
<td>-3.3/-2.9/-2.3</td>
<td>-3.4/-2.6/-1.6</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Continuous variables are displayed as 25th/50th/75th percentile.
Relation Between Positive Treadmill Test Response and Factors Associated With Myocardial Salvage in Patients With Restenosis

Among the 55 patients with interpretable treadmill tests and restenosis, 34 had occluded infarct arteries before angioplasty, 19 had patent arteries after thrombolytic therapy, and two had reperfused spontaneously without previous thrombolytic therapy (Table 5). Presence of collaterals did not affect the rate of subsequent positive treadmill tests: among the 34 patients whose arteries were initially occluded, collaterals were present in one of eight (12%) with positive tests and in three of 26 (12%) with nonpositive tests \( p > 0.90 \). Additionally, among the 34 patients with baseline occlusions, time to catheterization was similar among those with positive (median, 4.5 hours) and those with nonpositive tests (4.9 hours, \( p = 0.41 \)). Delay in thrombolytic treatment did not appear to be responsible for the inability to have an ischemic response in these patients since among the 19 patients who reperfused after thrombolytic therapy, the time from symptom onset to treatment was actually slightly longer among those with positive (median, 3.6 hours) than in those with nonpositive tests (2.4 hours, \( p = 0.01 \)). Among the 55 patients with restenosis, extent and severity of hypokinesis were similar between those with positive and those with nonpositive tests \( (p = 0.92 \) and \( p = 0.68 \), respectively).

Discussion

Our study demonstrated that anginal symptoms and the results of treadmill testing in follow-up had only a weak relation to restenosis in a population of patients who underwent angioplasty for acute myocardial infarction. Importantly, this finding is based on examination of a large consecutive population of patients with a high rate of angiographic follow-up. In addition, this study is the first to examine the use of follow-up treadmill testing for identifying restenosis in a population that underwent angioplasty in the setting of acute myocardial infarction.

Previous studies have demonstrated that acute myocardial infarction patients who have a residual subtotal stenosis in the infarct artery are more likely to develop ischemia on subsequent exercise testing. In a study of patients with acute myocardial infarction, exercise thallium imaging demonstrated greater residual peri-infarct ischemia in a group randomized to intracoronary streptokinase than in those randomized to emergency angioplasty. This effect was related to the greater residual stenosis of the infarct-related artery in the streptokinase group. Others have shown that angioplasty within the first few days after thrombolytic therapy for myocardial infarction improved the ejection fraction response to exercise as assessed by gated blood-pool imaging. These data support the concept that angioplasty reduces the extent of myocardial ischemia in the infarct artery distribution and that exercise-induced ST deviation might indicate recurrence of stenosis of this vessel. The present study used the treadmill test to examine this hypothesis because the treadmill is the test most often used by practicing physicians to follow patients after myocardial infarction.

We found the clinical value of exercise electrocardiography for detecting restenosis to be limited. ST deviation of 0.10 mV or more had only 24% sensitivity for the detection of restenosis in our population. The specificity of the test, or percent of patients without restenosis who had ST deviation less than 0.10 mV, was 88%. The more clinically relevant way to look at these tests is to calculate the likelihood of restenosis given a positive or negative test result. The negative predictive value (the probability of no restenosis among patients with ST deviation less than 0.10 mV) was 64% while the predictive value of a positive test was only 57%. More marked ST deviation, although uncommon, yielded more useful results: ST deviation more than 0.15 mV correctly predicted restenosis in seven of 10 patients or 70%, and among patients with ST deviation more than 0.20 mV, restenosis had occurred in three of three patients or 100%.

The reported sensitivity and specificity of exercise electrocardiography for detection of restenosis after elective angioplasty for ischemic heart disease have ranged from 15% to 78% and from 33% to 88%, respectively. Corresponding figures for exercise radionuclide angiography are 75–100% for sensitivity and 5–75% for specificity while exercise thallium scintigraphy in this setting has a reported sensitivity of 42–100% and a specificity of 46–100%. Factors contributing to this wide range of results include differences in the definitions of angiographic success, of restenosis, and of a “positive” test result. Additionally, in most studies symptomatic patients or those with ischemic exercise test results were more likely to undergo follow-up angiography; those who were not restudied either were not included or were counted as not having restenosis. Using the same definitions and methodology as the current study (including a 96% angiographic follow-up rate), Bengtson et al found the sensitivity of exercise treadmill testing to be 61% and the specificity to be 68% for detecting restenosis in patients who underwent elective angioplasty for ischemic coronary artery disease. We have shown previously that the sensitivity of the treadmill test is relatively low (48%) for detection of patients with stenosis in only a single vascular distribution. The treadmill test may have been more sensitive in the study of Bengtson because referral of patients for angioplasty was due to symptoms or the presence of an ischemic response to exercise. In the present study the treadmill test sensitivity was even lower (24%) than that seen in one-vessel disease patients with chronic stable angina, probably because myocardial necrosis had reduced the amount of residual...
viable myocardium available to develop an ischemic response.

The demonstration of exercise-induced ST segment deviation among those with restenosis suggests that viable myocardium remains in the vascular distribution of the infarct-related vessel in a significant proportion of these patients. Despite evidence of ischemia in the infarct-artery territory in patients with restenosis, attempts to correlate indices of infarct size with the likelihood of a positive response were unsuccessful. While both the extent and severity of regional hypokinesis have previously been correlated with infarct size, neither altered the likelihood of a positive treadmill test. Furthermore, factors previously associated with greater myocardial salvage after reperfusion therapy, such as shorter time delay in administration of thrombolytic agents in patients with successful thrombolysis and the presence of coronary collateral blood supply and early angioplasty among patients who were initially occluded, had no effect on treadmill ST response in this study. Potential limitations of this analysis include the small number of patients studied and the imperfection of these correlates with actual infarct size.

The high specificity of the test for restenosis in this postinfarct population was probably due in part to the aggressive approach to revascularization among patients in our institution, thereby reducing the number of incompletely revascularized multivessel disease patients who might develop an ischemic response from an undilated vessel. Before discharge most patients who presented to our hospital with acute myocardial infarction who had left main or multivessel disease, subsequent angina, or an ischemic response to exercise had already been triaged to coronary bypass surgery or staged multivessel angioplasty. Thus, only 19% of patients in our final study population had disease in a vessel other than the infarct artery as their only significant coronary disease at the time of follow-up. As a result an ischemic ST segment response to exercise occurred in only 12% of patients without restenosis, and only 40% of them had significant disease in another coronary artery. Additionally, although a strong correlation of ST deviation with number of diseased coronary vessels was evident, as in previously studied postinfarct populations, the majority of positive treadmill responses were associated with restenosis.

Treadmill test variables, such as exercise duration and maximal heart rate, that have less predictive power in routine treadmill testing were not significantly correlated with restenosis in this analysis. Angina at follow-up was less closely associated with restenosis ($p=0.04$) than was ST deviation ($p=0.02$) when considered alone, and neither this variable nor angina during the test was independently correlated with restenosis in the multivariable regression model once ST deviation was known. This finding may be related to the greater sensitivity of ST segment response than symptoms for the presence of ischemia.

In patients who had serial treadmill tests (predischarge and at follow-up), change to a positive test was expected to be due either to achievement of a higher exercise heart rate (due to taper of $\beta$-blockers and increased exercise duration), to the interim occurrence of restenosis, or to both. However, the results of predischarge testing added no additional information to that available from follow-up testing; the sensitivity and specificity of the follow-up test were similar regardless of whether predischarge testing was performed, and no patients with positive tests at follow-up had a positive test before discharge.

There are a few notable limitations of this study. First, our definitions, both of successful angioplasty and of restenosis, were dichotomous and were based on qualitative visual estimation of percent stenosis of the coronary luminal diameter. The definition of restenosis used in this study (75% or more luminal diameter stenosis) is only one of the many proposed definitions. To date, there is no consensus on the most appropriate definition for a study such as this. None of the commonly used definitions of restenosis incorporate the full range of information available from angiographic assessment of coronary stenosis, which is a continuous function. These definitions also fail to assess the true physiologic extent of the restriction of coronary blood flow or ischemia present. These variables might be better assessed in future studies with computer-assisted quantitative angiographic methods or techniques of metabolic imaging. Radionuclide perfusion or radionuclide ventriculographic studies at rest and during exercise to assist in assessing the functional significance of the stenosis were not available in our population.

Second, other treadmill variables with significant predictive value might have been gleaned from an analysis involving a larger patient population with more restenosis events, but it is unlikely that any individual variable would prove to be more important than exercise-induced ST deviation.

Third, since the publication of several reports that failed to show improvement in outcome following emergency angioplasty for acute myocardial infarction, many cardiologists now perform angioplasty for uncomplicated myocardial infarction largely on a deferred basis. There appeared to be no difference in enzymatic infarct size or in preservation of regional wall motion in patients who underwent an emergency versus a deferred procedure. Therefore, similar results to those in this report would be expected in patients undergoing a deferred procedure although this concept has not been specifically evaluated.

Finally, although overall coronary anatomy is a more important determinant of prognosis in patients with coronary artery disease than is information
gleaned from exercise treadmill testing,¹⁸ no study has addressed the relative importance of recurrent stenosis in a vessel supplying an area of infarction. It is entirely possible that the results of exercise testing provide more clinically useful information regarding prognosis and patient management than does knowledge of anatomic restenosis of the infarct-related artery. Unfortunately, lack of a consistent approach to management of patients with these lesions in the current study population prevents us from commenting on the prognostic importance of these restenosis events.

In summary, the exercise treadmill test was insensitive for the detection of restenosis in patients who had undergone emergency coronary angioplasty for myocardial infarction. The predictive value of the test result was poor, both for positive and nonpositive tests, although the test performed slightly better in the small subgroup (2–7%) with more marked ST deviation (>0.20 or >0.15 mV, respectively). Information on predischarge treadmill testing or anginal symptoms and treadmill test results at the time of follow-up added no significant information once ST deviation was known. Although the weak association of exercise-induced ST deviation with restenosis suggests that residual viable myocardium is preserved in the infarct-artery distribution, we were unable to detect any relation between ST deviation and factors previously associated with myocardial salvage. While these findings tend to diminish the perceived value of exercise electrocardiography in postinfarction populations such as this, they should not detract from use of this test in evaluating functional capacity, in directing exercise prescriptions for cardiac rehabilitation, or in assessing prognosis.

References
21. Reimer KA, Jennings RB: The "wavefront phenomenon" of myocardial ischemic cell death: II. Transmural progression of necrosis within a framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979;40:633–644


KEY WORDS • exercise tests • myocardial infarction • angioplasty • stenoses
Exercise treadmill testing is a poor predictor of anatomic restenosis after angioplasty for acute myocardial infarction.
M B Honan, J R Bengtson, D B Pryor, D S Rendall, R S Stack, T Hinohara, T N Skelton, R M Califf, M A Hlatky and D B Mark

Circulation. 1989;80:1585-1594
doi: 10.1161/01.CIR.80.6.1585

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/80/6/1585

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/