Exercise-Induced ST Segment Elevation 2 Weeks After Uncomplicated Myocardial Infarction: Contributing Factors and Prognostic Significance

DAVID E. HAINES, MD, GEORGE A. BELLER, MD, FACC, DENNY D. WATSON, PhD, DONALD L. KAISER, Dr PH, SHARON L. SAYRE, BSN, ROBERT S. GIBSON, MD

Charlottesville, Virginia

To define the prevalence and clinical significance of exercise-induced ST segment elevation during predischarge treadmill testing after uncomplicated acute myocardial infarction confirmed by serum MB creatine kinase (CK) activity, 241 consecutive patients were prospectively investigated with quantitative exercise thallium-201 scintigraphy, rest radionuclide ventriculography and coronary angiography at 10 ± 3 days. All patients received customary care, and in none was thrombolytic therapy or emergency coronary angioplasty employed.

Eighty-two patients (34%) had exercise-induced ST segment elevation of ≥1 mm above rest baseline. These patients were similar to the 159 patients without this finding with respect to history of prior infarction, the Norris coronary prognostic index, exercise duration, metabolic equivalents (METs) achieved and peak heart rate-blood pressure product. The frequency of inducible myocardial ischemia and extent of angiographic coronary disease was also comparable in the two groups. Findings associated with larger infarct size and transmural extent of infarction were more common in patients with exercise-induced ST segment elevation than in those without, including higher peak CK values (1,235 ± 1,037 versus 942 ± 915 μmol/min per liter, p < 0.026), lower left ventricular ejection fraction (43 ± 12 versus 51 ± 10%, p < 0.001), a higher prevalence of pathologic Q waves in ≥2 contiguous infarct-related leads (80 versus 55%, p < 0.001), more persistent thallium-201 defects (2.2 ± 1.1 versus 1.4 ± 1.1, p < 0.001), abnormally increased lung uptake of thallium (33 versus 18%, p < 0.01) and a greater number of akinetic or dyskinetic segments (3.2 ± 2.5 versus 1.4 ± 1.9, p < 0.001). Among all variables subjected to stepwise discriminant function analysis, the severity of wall motion abnormalities at rest was the strongest independent predictor of exercise ST segment elevation. During a median follow-up of 34 months individual nonfatal cardiac event rates were similar in the two groups, and mortality was 22% in patients with exercise ST segment elevation compared with 11% in those without this finding (p = 0.10, Kaplan-Meier method).

It is concluded that exercise-induced ST segment elevation 10 ± 3 days after uncomplicated myocardial infarction is common and associated with greater impairment of global and regional left ventricular function due to more extensive damage, rather than extent of underlying coronary artery disease or residual ischemia as assessed by exercise test or quantitative thallium-201 scintigraphic criteria.

(J Am Coll Cardiol 1987;9:996–1003)

Since 1979, exercise testing has been widely used to assess prognosis after acute myocardial infarction (1-5). In the early postinfarction period, exercise-induced ST segment elevation is often observed (6,7) and has been associated with residual ischemia (8,9), significant left ventricular wall motion abnormalities (10-13) and a higher incidence of cardiac events during follow-up (6,7,14). However, conflicting opinions still exist regarding the significance of this finding, and most previous studies are retrospective analyses of heterogeneous groups of patients with atherosclerotic heart disease.

In a previous study (2), we reported the clinical, angiographic, scintigraphic and 1 year follow-up data in 140 patients with uncomplicated infarction. We now report data on the prevalence and clinical significance of exercise-induced ST segment elevation from a total of 241 consecutive
patients entered into this ongoing prospective natural history study. The purpose of the present study, which includes patients who have been followed up for 1 to 5 years, was to identify factors that may contribute to this finding of exercise-induced ST segment elevation and to assess its impact on prognosis.

Methods

Study patients. The study group was selected from 362 consecutive patients admitted to our coronary intensive care unit who met the following criteria: 1) acute myocardial infarction diagnosed by typical history of chest pain and a diagnostic rise and fall of the serum creatine kinase (CK) MB isoenzyme; 2) age ≤ 65 years; 3) absence of significant valvular, congenital or cardiomyopathic heart disease or history of coronary bypass surgery; 4) absence of cardiogenic shock, ventricular septal defect or papillary muscle rupture; 5) absence of serious noncoronary disease that might limit long-term follow-up; and 6) willingness to undergo predischarge coronary angiography, quantitative thallium-201 scintigraphy and rest radionuclide ventriculography.

All 273 patients (73%) who gave written informed consent were considered candidates for predischarge treadmill exercise testing. However, rest or effort angina in the antecedent 4 days, persistent congestive heart failure, poorly controlled arrhythmias or musculoskeletal handicap precluded performing the stress examination in 32 (12%). Each of the remaining 241 patients met criteria for an uncomplicated infarction by the fifth hospital day (15) and none received thrombolytic therapy or angioplasty in the acute period. Finally, our subgroup of 241 study patients was representative of all patients at our institution with uncomplicated infarction and similar with respect to all clinical variables (16) to the 89 eligible patients who declined the invitation to participate.

Clinical evaluation. All patients were evaluated on admission and daily thereafter by a staff cardiologist and a research nurse for the duration of their hospitalization. Each patient was assigned to Killip class I, II or III by established criteria (17). Serum CK levels and the MB isoenzyme fraction were determined, and 12 lead electrocardiograms and complete clinical evaluations were performed on admission and serially thereafter as previously described (2). Postinfarction complications including angina pectoris, infarct extension, congestive heart failure, hypotension, ventricular tachycardia or fibrillation, heart block requiring pacemaker insertion, pericarditis or right ventricular infarction syndrome were screened for, evaluated and recorded. Patients received routine and customary care during hospitalization.

Predischarge exercise testing. An intravenous cannula was inserted before the test and baseline electrocardiograms (ECGs) were recorded with patients in the supine, sitting and standing positions, and after 30 seconds of hyperventilation. All patients exercised on a treadmill a mean of 10 ± 3 days after onset of infarction using methodology previously described (2). Before the exercise test, no attempt was made to alter medical therapy that was to be continued on a long-term basis. Exercise was discontinued after a peak heart rate of 120 beats/min or 5 METs was achieved, or if limiting symptoms or signs developed, including angina pectoris, dyspnea, fatigue, frequent (>10/min), multifocal or paired ventricular extrasystoles, ST segment depression ≥ 4 mm or a decrease in systolic blood pressure of ≥ 10 mm Hg below the peak blood pressure during the protocol. An intravenous dose of 1.8 to 2.1 mCi of thallium-201 was administered followed by a 10 ml saline flush as the patient approached either the target heart rate or work load or limiting symptoms and the exercise was continued as tolerated for 60 additional seconds. All patients were monitored continuously throughout exercise and recovery, and 12 lead ECGs were recorded at 1 minute intervals during exercise and at 1, 2, 3 and 5 minutes during recovery.

Significant ST segment depression was defined as ≥ 1 mm of horizontal or downsloping ST segment depression below the rest baseline measured 0.08 second from the J point in three consecutive beats. Significant ST segment elevation was defined as ≥ 1 mm ST segment elevation above the rest baseline measured at the J point. ST elevation and depression were defined as the summation of ST segment elevation or depression, respectively, in all 12 leads of the standard surface ECG.

Quantitative thallium imaging. Our thallium imaging protocol has been described in detail in previous reports (2). Briefly, after image acquisition, each segment on the early (10 minutes) and late (2 to 3 hours) postexercise scintigrams was analyzed and classified as: 1) normal: normal thallium-201 uptake and washout; 2) a redistributing defect: ≥ 25% decreased thallium uptake (≥ 35% in the inferior segment) on the initial image with reduction in the defect ratio between abnormal and normal regions on the delayed images; or 3) a persistent defect: 25 to 50% (mild) or ≥ 50% (severe) diminished thallium uptake by numerical analysis without redistribution (18). Lung thallium activity was evaluated visually by comparing the initial and delayed unprocessed anterior projection as previously described (19).

Multigated blood pool imaging. After the delayed thallium-201 images were obtained, equilibrium gated blood pool imaging was performed at rest using standard techniques (20) to determine left ventricular ejection fraction and segmental wall motion patterns. Ejection fraction was calculated from the 45° left anterior oblique projection without caudal angulation using an accepted volume count method. Wall motion was assessed qualitatively by dividing the left ventricle into 11 segments as previously described (20,21). Left ventricular wall motion was graded using a 5 point scale: -1 = hyperkinetic; 0 = not seen; 1 = normal; 2 = hypokinetic; 3 = akinetic; and 4 = dyskinetic. A re-
gional wall motion score was derived by summing the scores of individual segments. The wall motion index was then calculated as the total wall motion score divided by the number of segments analyzed (20).

Coronary angiography. Selective coronary angiography in multiple oblique projections was performed in all patients within 24 to 72 hours of exercise testing. Our criteria for angiographic extent of coronary disease have been previously described (16). Briefly, the location of significant stenoses (that is, \( \geq 50\% \) luminal narrowing) was recorded using the 15 segment model recommended by the American Heart Association (22). Multivessel disease was defined as a \( \geq 50\% \) luminal narrowing in two or more vessels. Only the most severe stenosis of the coronary artery segment was recorded and each patient was classified as having one, two or three vessel disease. The vessel considered responsible for the infarction was identified as the coronary artery supplying the area of maximal asynergy seen on the radionuclide ventriculogram and consistent with the ECG-determined site of acute infarction. The infarct vessel was considered to be patent if prompt anterograde flow of angiographic dye across the stenosis was demonstrated and filled the distal vessel.

Follow-up. After hospital discharge, all patients were referred to the care of their private physicians, who had access to all study results. No attempt was made to standardize therapy or regulate rehabilitation strategy. Each patient was asked to return to the Post-Myocardial Infarction Clinic at 3 months, then yearly for 5 years. For those patients not returning to the clinic at the designated time, follow-up information was collected by telephone interview. The necessary information was obtained in all patients.

During the median follow-up period of 34 months, we specifically attempted to determine the incidence of 1) cardiac death; 2) recurrent myocardial infarction; and 3) the development of rapidly progressive angina pectoris with minimal exertion (New York Heart Association class III) or angina at rest (class IV) of sufficient clinical concern to warrant hospitalization. Because we anticipated that the results of exercise testing, thallium-201 scintigraphy or coronary angiography might contribute to the decision to perform surgery, the follow-up period was terminated in the case of coronary bypass surgery or percutaneous transluminal coronary angioplasty. The diagnosis of recurrent myocardial infarction was established as previously described. Cardiac death was defined if the death was sudden, occurring within 1 hour of onset of symptoms, or if it was associated with other cardiac complications for which the patient had been hospitalized. For purposes of analysis, only one event, the most serious in the preceding order, was tabulated for each patient.

Data interpretation and statistical analysis. All test results were interpreted by two experienced physicians without knowledge of patient identity or results of other tests. In cases of discordant readings, a consensus interpretation with a third blinded observer present was used. Individual test data were compiled prospectively and stored in a computerized data bank. Continuous data are presented as mean values \( \pm \) SD. To determine differences between means of independent observation, a one-way analysis of variance and Duncan’s multiple range test were used to delineate the significance of any observed differences. Discrete variables were analyzed using contingency tables with an appropriate chi-square or Fisher’s exact test. Stepwise discriminant function analysis was performed to establish the relative contribution of individual factors on the prediction of exercise-induced ST segment elevation. Follow-up event rates were calculated using a Kaplan-Meier life table analysis.

**Results**

Of the 241 patients in this prospective cohort, 82 (34%) had significant exercise ST segment elevation during pre-discharge exercise testing after uncomplicated myocardial infarction (Group I). The remaining 159 patients had no significant ST segment elevation over rest baseline (Group II) by the criteria established.

Clinical characteristics. No significant differences between Groups I and II were found with respect to age (51 ± 9 versus 51 ± 8 years), sex (89 versus 83% male), number of atherosclerotic risk factors (2.1 ± 1.0 versus 2.4 ± 1.1) or antecedent history of angina pectoris (43% for

**Table 1. Admission and Serial Rest ECG Findings in Patients With and Without Exercise-Induced ST Segment Elevation**

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 82)</th>
<th>Group II (n = 159)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST elevation present (pts)*</td>
<td>63 (77%)</td>
<td>99 (62%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>No. of leads with ST elevation</td>
<td>3.2 ± 2.6</td>
<td>1.9 ± 1.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>ΣST elevation (mm)</td>
<td>8.5 ± 9.0</td>
<td>4.1 ± 5.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Q wave myocardial infarction (pts)</td>
<td>66 (80%)</td>
<td>88 (55%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Anterior infarct location (pts)†</td>
<td>50 (61%)</td>
<td>33 (21%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*One or more leads with \( \geq 1 \) mm ST segment elevation. †Defined as evolutionary changes in at least two of precordial leads V<sub>1</sub> through V<sub>6</sub>. pts = number of patients.
Table 2. Angiographic Findings in Patients With and Without Exercise-Induced ST Segment Elevation

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 82)</th>
<th>Group II (n = 159)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vessels with ≥50% stenosis</td>
<td>1.8 ± 0.9</td>
<td>1.8 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel disease (pts)</td>
<td>45 (56%)</td>
<td>93 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of proximal coronary segments with ≥50% stenosis</td>
<td>1.1 ± 0.7</td>
<td>1.1 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Patient infarct vessel (pts)</td>
<td>25 (31%)</td>
<td>60 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>Residual infarct vessel stenosis (%)*</td>
<td>93 ± 19</td>
<td>91 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal infarct vessel stenosis (pts)</td>
<td>55 (67%)</td>
<td>94 (59%)</td>
<td>NS</td>
</tr>
<tr>
<td>LAD infarct-related vessel (pts)</td>
<td>53 (65%)</td>
<td>41 (26%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Includes patients with complete coronary occlusion at time of angiography. LAD = left anterior descending coronary artery; pts = number of patients.

Coronary angiography (Table 2). When Groups I and II were compared, no significant differences were found in the number of diseased vessels per patient, the prevalence of a stenosis of ≥50% in proximal coronary segments or the degree of residual stenosis of the infarct-related vessel. In the group of patients with infarction in the left anterior descending artery zone, there was a higher prevalence of exercise-induced ST segment elevation (53 [56%] of 94 patients) compared with the right coronary artery zone infarction (18 [17%] of 107 patients) or left circumflex zone infarction (11 [27%] of 40 patients) (p < 0.0001).

Exercise test data. No significant differences between Groups I and II were noted with respect to exercise performance variables including METs achieved (4.2 ± 1.9 versus 4.2 ± 2.1), treadmill time (7.2 ± 4.2 versus 7.3 ± 4.3 minutes) and peak heart rate-systolic blood pressure product (15.6 ± 4.7 versus 15.6 ± 5.8 × 10^3). Group I patients had a slightly higher peak exercise heart rate than did Group II (116 ± 18 versus 110 ± 19 beats/min, p = 0.032) despite a similar peak work load achieved. It is important that, when indicators of exercise-induced myocardial ischemia were assessed, they were found to be similarly distributed between the two groups (Fig. 1).

Radionuclide studies. Patients with exercise-induced ST segment elevation had a greater number of persistent thallium-201 defects, as well as more severe (that is, >50% variety) persistent defects than those without this finding (Fig. 2). The number of redistributing defects per patient in Group I versus Group II was similar. Increased lung thallium uptake was more common in Group I than in Group II patients (33 versus 18%, p = 0.006), implying a greater reduction in left ventricular contractile reserve in Group I patients.

Radionuclide ventriculography demonstrated more severe rest wall motion abnormalities in patients with exercise-induced ST segment elevation than in patients without this finding (Fig. 3), with a higher prevalence of akinetic or dyskinetic segments and a higher regional wall motion index score. The left ventricular ejection fraction was lower in Group I versus Group II patients.

Discriminant function analysis (Table 3). The number of akinetic or dyskinetic segments per patient, an infarct-
related left anterior descending artery and the presence of new Q waves associated with the index infarction were the only independent predictors of exercise ST elevation. Of these, the strongest predictor was the severity of rest segmental wall motion abnormalities. Although other factors such as peak CK level, ST segment elevation on the admission ECG and the presence of persistent thallium defects were strongly associated with exercise-induced ST segment elevation, they did not carry independent predictive value when the influences of these factors were removed. Factors associated with ischemia, such as exercise-induced angina, ST segment depression and redistribution of thallium-201 during serial postexercise imaging, were not significant predictors of exercise-induced ST segment elevation.

**Follow-up.** During follow-up (median 34 months), the nonfatal cardiac event rates were similar in Groups I and II including recurrent infarction (11 versus 10%), unstable angina pectoris requiring rehospitalization (26 versus 26%) and need for coronary revascularization (21 versus 25%, p = NS). There were a total of 21 cardiac deaths, 11 in Group I and 10 in Group II. When cardiac mortality was examined in a life-table analysis, a trend toward increased mortality was seen in Group I patients (Fig. 4). However, the number of patients was too small to achieve statistical significance.

**Discussion**

The present study examines a consecutive series of patients after uncomplicated acute myocardial infarction who were prospectively evaluated as part of an ongoing natural history study. The prevalence of exercise-induced ST segment elevation at 10 ± 3 days was relatively high, that is, 34%, and was correlated with ST segment elevation on the admission ECG. These patients also had higher peak CK values, a higher peak Killip class and a greater prevalence of Q wave infarction. Predischarge studies demonstrated more extensive and severe abnormalities in global and regional left ventricular function and more persistent thallium perfusion defects, implying greater infarct-related myocardial necrosis. Of interest, the angiographic extent of disease was found to be similar between patients with and without exercise-induced ST elevation. Moreover, no differences between groups were observed in the severity or proximity of the infarct-related vessel stenosis. If severe exercise-induced transmural ischemia was a dominant cause of exercise-induced ST elevation after myocardial infarction, one might have expected that patients exhibiting this finding would have a more narrowed infarct-related coronary stenosis. Our data show no difference in stenosis diameter of the infarct-related vessel between Groups I and II.

**Previous studies.** Investigators who have examined exercise-induced ST elevation have presented studies with pre-
Exercised-induced ST segment elevation was not observed in all patients with Q wave infarction, severe wall motion abnormalities or large, persistent thallium perfusion defects. It was more prevalent in patients with anterior myocardial infarction associated with left anterior descending artery occlusion than in patients with other infarct locations. A correlation of the presence and magnitude of ST elevation between the admission rest ECG and the predischARGE ECGs was also observed. The variable sensitivity of the surface ECG in the detection of regional myocardial events has been documented, as illustrated by its lower sensitivity in the diagnosis of acute posterior wall versus anterior wall myocardial infarction (33,34). This same phenomenon may apply to exercise-induced ST elevation with a correspondingly variable incidence of this finding depending on the location of prior infarction.

As noted by previous investigators (4,6,7,11,21,22), exercise-induced ST elevation is more often related to left ventricular dysfunction associated with severe wall motion abnormalities, as opposed to exercise-induced ST segment depression, which is more commonly associated with ischemia. Our findings are concordant with earlier studies in that no variable indicative of ischemia was significantly more common in the group with exercise-induced ST elevation versus the group without this finding. This included the stress test variables of exercise-induced chest pain, ST depression and thallium-201 redistribution, as well as multivessel disease at angiography.

Clinical outcome. During long-term follow-up, we found that the total and individual nonfatal cardiac event rates were similar in our two groups of patients. This observation is not surprising because the majority of all cardiac events in the present study were related to recurrent ischemia and the exercise scintigraphic evaluations performed before hospital discharge demonstrated that the two groups were compa-
rable in the amount of residual postinfarction ischemia. Unlike previous investigators (7,28), we did not show a significantly higher mortality risk in patients with exercise-induced ST segment elevation. In part, this may be due to the nature of our study group and the low overall death rate, that is, 8.7% (5.0% for sudden death) during follow-up. It is important to again emphasize that all of our patients who met criteria for an uncomplicated infarction were eligible for exercise testing at 10 ± 3 days and had a mean ejection fraction of 49 ± 11%. Moreover, only 50 (21%) of the 241 patients had ejection fraction values <40% and none exhibited signs of congestive heart failure beyond the fifth hospital day after onset of infarction. Because there were only 12 sudden, presumably arrhythmogenic deaths in our entire cohort, our study may not have the power (35) to reveal a significant correlation between exercise-induced ST segment elevation and subsequent mortality.

Mechanisms of exercise-induced ST elevation. The precise mechanism of exercise-induced ST segment elevation is still poorly understood. Experimental models of transmural infarction have demonstrated increasing ST segment changes with increasing paced heart rate as assessed by isopotential mapping (36). Theoretically, after the occurrence of transmural myocardial injury, epicardial action potential duration shortens and its amplitude diminishes. During diastole, injured myocardium is able to maintain a less negative transmembrane potential. The combination of these phenomena in regions contiguous to healthy myocardium will lead to ST segment elevation and TQ segment depression. Both of these phenomena would be accentuated with increasing heart rate leading to augmentation of rest ST segment elevation with exercise. Other yet undefined mechanisms may also play a role, particularly those involving consideration of geometric changes in the infarct segment relative to the chest wall during exercise.

Summary and clinical implications. The present prospective study examined multiple clinical, functional (that is, scintigraphic) and angiographic variables that might contribute to exercise-induced ST segment elevation 10 ± 3 days after uncomplicated acute myocardial infarction. Our data indicate strong correlations with factors associated with greater transmural myocardial damage rather than residual ischemia or more extensive underlying coronary artery disease. Nonfatal cardiac events that were predominantly ischemic in nature were not more prevalent in patients with exercise-induced ST segment elevation. Although a trend toward increased mortality was observed, the low number of cardiac deaths in follow-up overall in this group of patients with uncomplicated myocardial infarction and the small sample size did not allow us to statistically confirm the significance of this finding. However, our mortality data parallel findings in other studies showing a worse prognosis in patients with more impaired left ventricular function. These findings suggest that patients with uncomplicated infarction and isolated exercise-induced ST segment elevation, without evidence of specific markers of ischemia, do not require additional evaluation such as early catheterization or a more aggressive treatment strategy aimed at augmenting nutrient blood flow reserve.

We thank Elizabeth Howk for her excellent assistance in preparing this manuscript.

References


