CLINICAL STUDIES

Comparison of Clinical Variables and Variables Derived From a Limited Predischarge Exercise Test as Predictors of Early and Late Mortality After Myocardial Infarction

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An exercise test limited to 5 METS or 70% of age-predicted maximal heart rate was performed 1 day before hospital discharge by 225 survivors of acute myocardial infarction, all of whom were subsequently followed up for at least 5 years. The mortality rate was 11.1% during the first year, but averaged only 2.9% per year from the second to fifth year. Over the entire follow-up period, the five variables that predicted mortality by multivariate analysis were QRS score, an exercise-induced ST segment shift, previous infarction, failure to achieve target heart rate or work load and ventricular arrhythmia during the exercise test. Because mortality differed markedly before and after 1 year, Cox regression analyses were performed separately for both of these periods.

The factors that were predictive of mortality during the first year were an exercise-induced ST shift ($p < 0.0001$, relative risk 7.8), failure to increase systolic blood pressure by 10 mm Hg or more during exercise ($p = 0.0039$, relative risk 4.3) and angina in hospital 48 hours or longer after admission ($p = 0.0046$, relative risk 3.4). None of these three variables was predictive of mortality after 1 year. Previous infarction ($p = 0.0007$), QRS score ($p = 0.0042$) and ventricular arrhythmia during the exercise test ($p = 0.016$) were predictive of mortality after the first year.

Thus, clinical and exercise test variables are complementary predictors of mortality after myocardial infarction. An abnormal ST segment response during an early limited exercise test and angina in the hospital are common strong predictors of mortality to 1 year, but not thereafter. Late mortality correlates with markers of poor left ventricular function.

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A limited exercise test performed soon after myocardial infarction predicts subsequent prognosis (1–6). Exercise-induced ST segment depression (1,2), ventricular arrhythmia during the test (3,5) and a limited exercise tolerance (3,4) have been associated with an increased risk. However, the relative importance of these prognostic variables and their relation to other clinical variables that predict prognosis are uncertain. Thus, the role of a limited exercise test after myocardial infarction remains incompletely defined (7–10).

In some studies of prognosis after infarction, death, reinfarction, unstable angina, stable angina and coronary artery bypass surgery are analyzed together as end points, even though their causative mechanisms are probably dissimilar. Limitations of other studies include small patient groups and short follow-up periods so that few patients reach clear-cut end points such as death or reinfarction. Survival after hospital discharge is nonlinear (9,11,12); mortality during the first year approximates 10%, but decreases to 3 to 5% per year thereafter. When risk changes, the factors that predict it also probably change; however, any such differences have not been investigated previously.

This study was undertaken to clarify some of these problems. A large series of patients who had a limited exercise test before hospital discharge after infarction were followed up for a minimum of 5 years. Clinical and exercise test variables were compared to determine their relative ability to predict 5 year survival. In addition, the influence of these variables during the first year of follow-up study, a high

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risk period, was compared with their effect during the second to fifth years when risk was lower.

Methods

Patient selection. Acute myocardial infarction was diagnosed when two of the following three criteria were present: 1) myocardial ischemic pain lasting longer than 30 minutes: 2) increase above twice the upper limit of normal of two of the three serum cardiac enzymes (lactate dehydrogenase, aspartate aminotransferase or creatine kinase with its MB isoenzyme): and 3) Minnesota code electrocardiographic criteria (13) for acute myocardial infarction. When only ST and T wave abnormalities were present without new Q waves, "a non-Q wave" infarction was diagnosed.

A consecutive series from 1976 to 1977 of 225 patients who had a limited exercise test before hospital discharge after myocardial infarction formed the study group. This group overlaps with, but is not identical to, other study groups described in previous reports from our institution (1,14). Excluded were patients older than 70 years of age, those with overt heart failure (pulmonary rales and sinus tachycardia, or a third heart sound), those with chest pain within 4 days of testing, those with a physical handicap that precluded testing and those who refused to provide informed consent. During this period, 12% of all patients admitted with myocardial infarction died in the hospital, 28% were excluded and 60% were tested.

Exercise protocol. The exercise test procedure has been described in detail elsewhere (1,14). Tests were performed 1 day before hospital discharge, a mean of 11 days (range 7 to 20) after the onset of infarction. By this time, patients had progressed to an activity level at which they walked freely in the hospital ward and climbed one flight of stairs. At the time of the test, 136 patients (60%) were receiving no cardiac drugs, 71 (32%) were taking a beta-receptor blocking agent, 13 (6%) were taking digitalis and 5 (2%) were taking a combination of the two drugs. No drug was withheld or altered in dosage for exercise testing.

Tests were performed on a treadmill using the Naughton protocol (15). During the test and for 5 minutes thereafter, lead CM_5 was continuously monitored and recorded along with cuff blood pressure at each minute. End points were 70% of age-predicted maximal heart rate (16), 5 METS (according to the Naughton protocol), the appearance of important ventricular arrhythmia, angina, severe fatigue or dyspnea and greater than 5 mm of ST segment displacement compared with the rest tracing. A test was considered abnormal if 1 mm or more of ST segment depression or elevation developed compared with the baseline tracing. All tests were interpreted in a blinded fashion without knowledge of the clinical data. No complications resulted from the exercise tests.

Follow-up. At 3, 6 and 12 months after infarction, a clinical history, physical examination and electrocardiogram were obtained from each patient during a visit to the hospital. The intervals between subsequent visits varied according to clinical status. No patient was lost to follow-up. Survivors were followed up for a minimum of 5 to a maximum of 7 years. Thirty-six patients (16%) had coronary artery bypass surgery, usually for angina that could not be controlled by medical treatment. Exercise test results did not appear to influence the frequency of bypass surgery; 5 (18%) of 28 patients with ST segment elevation, 14 (20%) of 69 with ST depression and 17 (13%) of 128 with no ST change during exercise underwent surgery during the follow-up period (p = NS). Although the results of the exercise test were available to the treating physician, they did not seem to exert an important effect on therapeutic decisions, in the first year because the prognostic value of the test had not been established and thereafter because most patients were in stable condition.

Data analysis (Table 1). The clinical variables analyzed included age, sex, previous myocardial infarction, type and electrocardiographic site of infarction, recurrence of myocardial ischemic pain in the hospital more than 48 hours after admission and treatment with beta-receptor blocking drugs or digitalis at discharge. A QRS scoring system that estimates infarct size from a standard 12 lead electrocardiogram, as refined by Wagner et al. (17), has been shown to correlate with both the anatomic extent of infarction (18), postinfarction ejection fraction (19) and infarct size as assessed by thallium-201 perfusion defect (20). The QRS score for all patients was calculated from an electrocardiogram recorded between 7 and 10 days after hospital admission, excluding residual abnormalities from previous infarctions.

The exercise test variables analyzed in addition to ST segment shifts were the appearance of any ventricular arrhythmia during or immediately after exercise, failure of systolic blood pressure to increase by 10 mm Hg or more during the test and failure to achieve the target heart rate or work load. Patients with ST depression or elevation were grouped together and compared with patients with no ST shift during exercise.

Statistical analysis. *Mortality curves* were constructed using the Kaplan-Meier product-limit method and compared by log-rank test for discrete variables (21) and the Cox model with one beta parameter for continuous variables (22). Variables significant by univariate analysis were analyzed with Cox's regression model (22); the variables retained in the model were selected in a stepwise manner, a likelihood ratio test being performed on the partial likelihood functions to test the significance of each candidate variable (23).

In its simplest formulation, the Cox model is called the proportional hazard model and it assumes that the relative risk associated with any fixed covariate is constant over time. However, because risk after myocardial infarction is not constant (9,11,12), multivariate Cox's regression analysis was repeated, estimating separately relative risks for 1 year or less and greater than 1 year mortality (24). Mortality to 1 year was analyzed by eliminating all follow-up data after 1 year; mortality after 1 year was analyzed separately, omitting the patients who died before 1 year.

Results

Clinical features (Table 1). The mean age (±standard deviation) of the patients tested was 52 ± 9 years; 57 (25%) of the 225 had had a previous myocardial infarction. Only 30 of the patients (13%) were women. Non-Q wave infarction occurred in 47 patients (21%); the electrocardiographic site of myocardial infarction was anterior in 97 (43%) and inferior in 123 (55%). Fifty-two patients (23%) had angina in the hospital more than 48 hours after admission. The mean QRS score for the group, including patients with a non-Q wave infarction, was 4.2 ± 3.9.

Exercise test results. The exercise test induced ST segment depression in 69 patients (31%) and ST elevation in 28 (12%). The remaining 128 patients (57%) had no ST segment change during exercise. The QRS score was lower in patients with ST depression (2.7 ± 2.8) and higher in patients with ST elevation (8.9 ± 4.6) compared with that in patients without ST segment displacement during exercise (4.0 ± 3.6) ($p < 0.005$). The test provoked ventricular arrhythmia in 44 patients (20%); in each instance, the arrhythmia disappeared without specific treatment. The target heart rate (70% of age-predicted maximal heart rate) or work load (5 METS) was achieved by 166 patients (74%). Twenty patients (9%) failed to increase systolic blood pressure by at least 10 mm Hg during the test.

Predictors of mortality. During the entire follow-up period of 5 to 7 years, 58 (26%) of the 225 patients died, (51 [23%] within 5 years and 25 [11%] within 1 year). Death was sudden in 31 patients (53%), as a result of recurrent infarction in 17 (29%), heart failure in 6 (10%) and other conditions in 4 (7%).

The eight variables that correlated with mortality by univariate analysis are listed in Table 2. Four of these variables are clinical: previous myocardial infarction, QRS score, angina 48 hours or more after hospital admission and electrocardiographic site of infarction. The other four are derived from the predischarge exercise test. The strongest predictors were an ST segment shift during exercise ($\chi^2 = 20.4$, $p < 0.0001$) and a history of previous infarction ($\chi^2 = 17.8$, $p < 0.0001$).

Figure 1 illustrates the mortality curves to 5 years determined by using the Kaplan-Meier product-limit method,

Table 1. Distribution of Clinical and Exercise Test Variables in the 225 Study Patients

Age (yr)*	52 ± 9
Sex	
Male	195 (87%)
Female	30 (13%)
Previous infarction	57 (25%)
Type of infarction	
Q wave	178 (79%)
Non-Q wave	47 (21%)
ECG site of infarction	
Anterior	97 (43%)
Inferior	123 (55%)
Indeterminate	5 (2%)
Angina 48 hours or longer after admission	52 (23%)
QRS score*	4.2 ± 3.9
Drugs at time of test	
None	136 (60%)
Beta-receptor blocking agents	71 (32%)
Digitalis	13 (6%)
Both	5 (2%)
ST segment during test	
Depression (≥1 mm)	69 (31%)
Elevation (≥1 mm)	28 (12%)
No change	128 (57%)
Ventricular arrhythmia during test	44 (20%)
Target HR or work load achieved	166 (74%)
Failure to increase systolic BP by 10 mm Hg or more	20 (9%)

*Data are mean ± standard deviation. BP = blood pressure; ECG = electrocardiographic; HR = heart rate.

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Table 2. Clinical and Exercise Test Predictors of Mortality by Univariate Analysis for Entire Follow-up Period

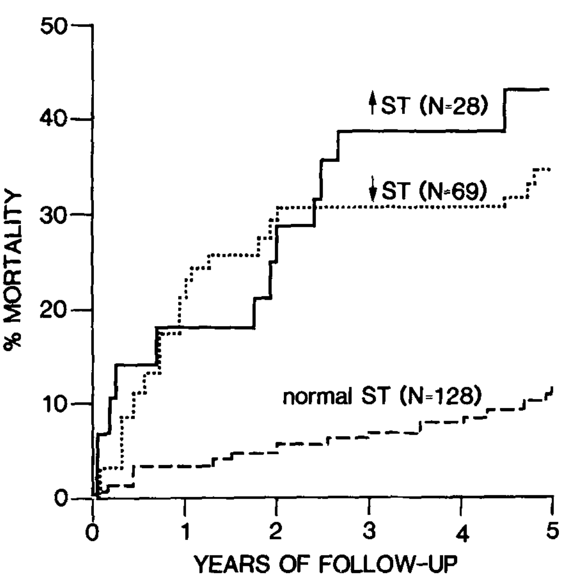
Variable	Chi-Square	p Value
Exercise-induced ST shift	20.4	<0.0001
Previous infarction	17.8	<0.0001
Target HR or work load not achieved	14.3	<0.001
Ventricular arrhythmia during test	11.3	<0.001
QRS score	10.0	<0.01
Angina 48 hours or longer after admission	7.5	<0.01
Failure to increase systolic BP by 10 mm Hg or more	7.0	<0.01
ECG site of infarction (anterior vs. others)	6.0	<0.05

Abbreviations as in Table 1.

with patients grouped according to ST segment response to exercise. At 1 year, 4 (3%) of the 128 patients with no ST segment change during exercise, 16 (23%) of the 69 with ST depression and 5 (18%) of 28 with ST elevation had died. At 5 years, the cumulative mortality rate was 12% (15 of 128) in the group with no ST changes, 35% (24 of 69) in the group with ST depression and 43% (12 of 28) in those with ST elevation (overall $p < 0.0001$).

A history of previous myocardial infarction discriminated between survivors and nonsurvivors (Fig. 2). At 1 and 5 years, respectively, the mortality rate was 18% (10 of 57) and 40% (23 of 57) in patients with previous infarction compared with 9% (15 of 168) and 17% (28 of 168) in those without.

Figure 1. Mortality during a 5 year follow-up study of patients with no ST shift during a limited exercise test performed before hospital discharge (normal ST), patients with ST depression during the test (↓ ST) and patients with ST elevation (↑ ST) using the Kaplan-Meier product-limit method. Differences between the group with ST depression and the group with ST elevation are not statistically significant; however mortality in both of these groups differs significantly from that in the group with a normal ST response ($p < 0.0001$).



Cox regression analysis was performed to determine which of the eight variables predictive of mortality by univariate analysis were also predictive by multivariate analysis (Table 3). The five variables that remained statistically significant, in order of rank, were QRS score, exercise-induced ST shift, previous infarction, target heart rate or work load not achieved and ventricular arrhythmia during the exercise test. Three variables that were predictive of mortality by univariate analysis were not retained by multivariate analysis: failure to increase systolic blood pressure by 10 mm Hg or more, angina 48 hours or more after hospital admission and the electrocardiographic site of infarction.

Time-dependent analysis of predictors. The mortality rate during the first year of follow-up was 11% (25 of 225), but averaged only 3% per year from the second to fifth year. Because of this difference, Cox regression analyses were done separately for the periods from discharge to 1 year and from 1 year to the end of follow-up (5 to 7 years). The

Figure 2. Mortality during a 5 year follow-up study of patients with and without previous myocardial infarction (MI) using the Kaplan-Meier product-limit method ($p < 0.0001$).

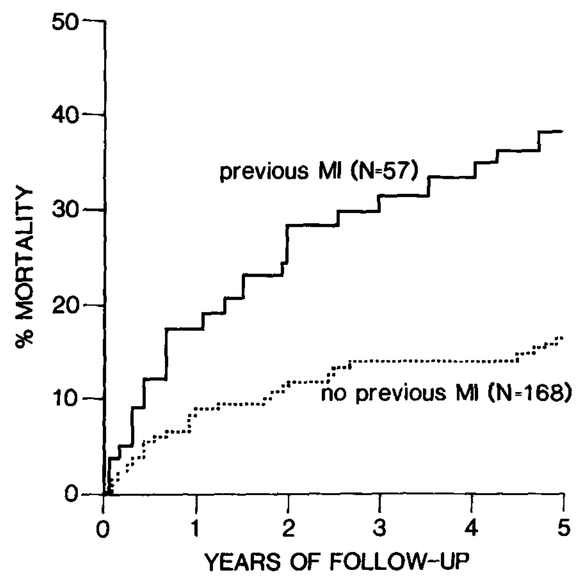


Table 3. Predictors of Mortality for Entire Follow-up Period by Cox Regression Analysis

Variable	Chi-Square	p Value	Relative Risk
QRS score	10.6	0.0012	–
Exercise-induced ST shift	9.5	0.0020	2.4
Previous infarction	7.9	0.0049	2.2
Target HR or work load not achieved	6.4	0.012	2.1
Ventricular arrhythmia during test	5.6	0.018	2.0
Variables predictive by univariate analysis only			
Failure to increase systolic BP by 10 mm Hg or more	2.5	0.12	–
Angina 48 hours or longer after admission	2.3	0.13	–
ECG site (anterior vs. others)	0.2	0.67	–

Relative risk not calculated for continuous variables (QRS score) or for variables that were not statistically significant. Abbreviations as in Table 1.

variables that were predictive of mortality during these two periods were strikingly different (Table 4). During the first year, the strongest predictor was an exercise-induced ST shift ($\chi^2 = 20.0$, $p < 0.0001$). Failure to increase systolic blood pressure during exercise and angina 48 hours or longer after admission were also predictive, but the other variables were not.

For the rest of the follow-up period, the three variables that were predictive of mortality during the first year do not remain predictive, but are replaced by three variables that were not predictive during the first year. Two of these variables are clinical (a history of previous infarction and QRS score); the third is ventricular arrhythmia during the exercise test.

Discussion

Survivors of myocardial infarction comprise a large, readily identifiable subset of patients with coronary artery disease with a relatively high short-term mortality rate. Strategies to improve their survival include medical treatment with beta-receptor blocking agents (25) or other drugs (26,27) and identification of high risk patients who might benefit from specific but not necessarily uniform therapy. High risk patients can be detected on the basis of clinical characteristics (28–30), electrocardiographic monitoring (31,32), exercise testing with (33,34) or without (1–6) thallium-201 or radioisotopic ventriculography, coronary arteriography (34–36), and other means (37–40). The extent and severity

Table 4. Differences in Predictors of Mortality by Cox Regression Analysis During First Year of Follow-up Compared With After 1 Year

	Chi-Square	p Value	Relative Risk
Variables predictive during first year			
Exercise-induced ST shift	20.0	<0.0001	7.8
Failure to increase systolic BP by 10 mm Hg or more	8.3	0.0039	4.3
Angina 48 hours or longer after admission	8.0	0.0046	3.4
Variables not predictive during first year			
QRS score	3.5	0.062	–
Ventricular arrhythmias during test	1.9	0.17	–
Previous infarction	1.3	0.25	–
Target HR or work load not achieved	1.0	0.32	–
ECG site of infarction (anterior vs. others)	0.1	0.76	–
Variables predictive after first year			
Previous infarction	11.4	0.0007	3.5
QRS score	8.2	0.0042	–
Ventricular arrhythmia during test	5.8	0.016	2.7
Variables not predictive after first year			
ECG site of infarction (anterior vs. others)	3.8	0.050	–
Target HR or work load not achieved	2.1	0.15	–
Exercise-induced ST shift	1.1	0.31	–
Angina 48 hours or longer after admission	0.03	0.87	–
Failure to increase systolic BP by 10 mm Hg or more	0.01	0.98	

Relative risk not calculated for continuous variables (QRS score) or for variables that were not statistically significant. Abbreviations as in Table 1.

of coronary obstructive disease and the degree of left ventricular dysfunction are the two primary factors that influence outcome (36); however, in most survivors of infarction risk can be accurately assessed without coronary arteriography (9,10). This study compares clinical predictors and variables derived from a limited exercise test performed before hospital discharge, using mortality as the end point, with follow-up complete to 5 years.

Early mortality. During the first year, the three independent predictors of mortality were an exercise-induced ST shift, failure to increase systolic blood pressure during exercise and angina during hospitalization. Exercise-induced ST depression (present in 31% of the study group) and angina during hospitalization (present in 23%) indicate recurrent myocardial ischemia, a factor that is therefore closely linked to mortality during the first year after myocardial infarction. These two variables are quite independent of each other ($r = 0.06$), probably because after infarction, transient ST depression either at rest or during exercise (1) often occurs without angina and vice versa. The other factors correlating with mortality during the first year are less common and their underlying mechanisms are more complex. Exercise-induced ST elevation (present in 12% of the patients) is probably caused by left ventricular dysfunction more often than by ischemia (41). QRS score, a rough estimate of infarct size, was significantly higher in patients with ST elevation and significantly lower in patients with ST depression as compared with those without ST abnormalities during exercise. An inadequate blood pressure response to exercise may sometimes be related to ischemia because it may disappear after successful bypass surgery (42), but it may also be caused by poor left ventricular function or other factors.

The correlation between indicators of recurrent myocardial ischemia and early mortality after infarction is clinically relevant because recurrent myocardial ischemia is usually amenable to medical or surgical treatment. Although treatment has not been shown to improve survival in the specific subset of patients with exercise-induced ST depression on a limited exercise test soon after infarction, in our view their poor prognosis justifies coronary arteriography before hospital discharge in nearly all cases.

Comparison with previous studies. In 70 patients with angina within 10 days of infarction, accompanied by electrocardiographic changes, Shuster and Bulkley (43) observed a 56% mortality rate during a mean follow-up of 6 months. Our patients with angina in hospital had a better prognosis than this, probably because electrocardiographic changes were not required during angina and because the sickest patients were excluded from exercise testing.

In studies of the prognostic determinants after myocardial infarction, mortality rates depend on patient selection and vary widely. In studies requiring coronary arteriography, a low mortality was reported: 5% (7 of 140) to 15 months (34), 6% (11 of 179) to 28 months (35) and 7% (19 of 259) to 34 months (36). When only clinical variables are evaluated, mortality rates tend to be higher; for example, 15% (15 of 100) to 6 months (28), 16% (35 of 221) from 30 days to 26 months (29) and 19% (11 of 57) to 1 year (39). Some studies of exercise testing after infarction reported a high mortality rate (11% to 1 year in our study and 9% [21 of 236] for 1 year cardiac mortality in the report of Weld et al. [3]). In contrast, in a study by DeBusk et al. (44), mortality to 6 months was only 2% (7 of 338); however, 327 of 665 patients were excluded from testing because their risk was already known to be increased due to the presence of historic or clinical risk factors.

For this reason, different studies cannot be easily compared. The results of exercise testing are also influenced by concomitant drug therapy, the end points selected for the test and the number of electrocardiographic leads recorded (41). Despite these problems, most studies of patients with infarction confirm that exercise-induced ST depression is of prognostic importance (2,6,44,45). In the study of Weld et al. (3), this finding was associated with a higher mortality rate (13.5% [7 of 52] compared with 8% [14 of 183]), but the difference was not statistically significant. Weld et al. concluded that a larger difference was not found because more of their patients may have stopped exercise early because of symptoms of heart failure. Exercise-induced ST depression is also a strong predictor of mortality in patients with known coronary disease without infarction (46).

The inclusion in our study of relatively high risk patients, such as those with angina in hospital, appears to be justified because exercise testing caused no complications and the test provided additional independent prognostic information. Indeed, by multivariate analysis, exercise-induced ST shift was the strongest predictor during the first year with a relative risk of 7.8.

Limitation. A limitation of this study is that only one electrocardiographic lead, CM_5, was recorded during exercise. In most subsets of patients with coronary disease, increasing the number of leads being monitored increases the frequency of positive tests (41,47,48). However, the purpose of exercise testing after infarction is to identify high risk patients, not to predict which patients have underlying coronary disease. Using more leads in this study might have decreased the prognostic value of an abnormal ST segment response.

Late mortality. In our study group, the mortality rate decreased from 11% in the first year after infarction to an average of 3% per year during the next 4 years. A multivariate analysis limited to this later period showed that the three variables that were independent predictors of mortality during the first year were of no predictive value thereafter. Instead, previous infarction, QRS score and ventricular arrhythmia during the exercise test done before discharge predicted mortality after 1 year by multivariate analysis. In other studies (29,30,44), previous myocardial infarction has been shown to correlate with a worse survival. In the Coronary Drug Project (30), patients with and without this finding had a 32 and 18% 5 year mortality rate respectively ($p < 0.01$), similar to the 40 and 17% 5 year mortality rate in this study. The difference was attributed to poorer left ventricular function in patients with previous infarction (30). QRS score probably also reflects the degree of left ventricular dysfunction (18–20).

Exercise-induced ventricular arrhythmia. This is considered to be a clinical marker of left ventricular dysfunction (49), but in some cases it may be due to myocardial ischemia. A weak but statistically significant positive correlation ($r = 0.15$, $p < 0.05$) between exercise-induced ventricular arrhythmia and ST depression was present in this study. In the large series of patients reported by Califf et al. (49), exercise-induced ventricular arrhythmia correlated with more severe coronary disease, worse left ventricular function and poorer survival; it added significant prognostic information when only noninvasive characteristics were evaluated, but not when the results of coronary and left ventricular angiography were taken into account (49).

In the study of Weld et al. (3), ventricular arrhythmia during the exercise test was predictive of subsequent mortality; however, in most other studies of exercise testing after infarction, such a correlation was not found. The presence and complexity of ventricular arrhythmias recorded by Holter monitoring after infarction are associated with increased mortality during follow-up (31,32).

Left ventricular dysfunction. Although the factors that predicted late mortality in this study are all indicators of poor left ventricular function, the mechanism of death usually was not severe heart failure. Death was most often sudden or due to recurrent infarction.

The factors that predicted late mortality in this study were also independent predictors over the entire follow-up period, but not when the analysis was restricted to the first year. The QRS score almost attained statistical significance ($p = 0.06$) as an independent predictor during the first year after infarction. Patients with overt heart failure at the time of hospital discharge were excluded from this study. Variables that reflect poor left ventricular function would likely correlate better with mortality in a study group that included such high risk patients.

Clinical implications. For practical purposes, previous infarction, a high QRS score and exercise-induced ventricular arrhythmia should be viewed as indicators of a poor prognosis from hospital discharge to at least 5 years thereafter. In contrast, angina in the hospital and exercise-induced ST shifts on a limited exercise test done before discharge delineate a subgroup with a high 1 year mortality, probably related to recurrent ischemia. Clinical variables and variables derived from a limited exercise test performed before hospital discharge after myocardial infarction are complementary predictors of subsequent mortality.

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