The changing role of the exercise electrocardiogram as a diagnostic and prognostic test for chronic ischemic heart disease

BERNARD R. CHAITMAN, MD, FACC
St. Louis, Missouri

The exercise electrocardiogram has been the subject of intense research over the last 50 years, as both a diagnostic and prognostic method to assess patients with chronic ischemic heart disease. In 1986, the strengths and limitations of the technique to predict coronary and multivessel disease in clinical patient subsets are understood. The diagnostic accuracy of the test is improved by consideration of Bayesian theory, multivariate models and new non-ST segment criteria. Post-test coronary disease risk estimates are best reported in terms of a conditional probability, rather than statements of "positive" or "negative."

The clinical indications for exercise testing as a diagnostic and prognostic method to assess patients with chronic ischemic heart disease have evolved in the last 30 years. New information resulting from electrocardiographic/angiographic correlative studies, prognostic stratification of clinical patient subsets according to exercise test results and the increasing role of newer noninvasive methods that supplement the information obtained from exercise testing and that are useful in calibrating the functional significance of certain electrocardiographic findings have markedly enhanced the clinical utility of the test. In 1986, exercise testing is most useful in the prognostic assessment of patients with ischemic heart disease, evaluation of the efficacy of antianginal therapy or revascularization procedures, documentation and characterization of cardiac arrhythmias and evaluation of patients with chest pain. Exercise testing is finding increased use in the evaluation of patients with pulmonary disease, chronic congestive heart failure and peripheral vascular disease (1–9).

Many physicians have become disillusioned with the diagnostic content of the exercise electrocardiogram. However, exercise electrocardiography remains an important, relatively inexpensive and widely used technique in the routine assessment of patients with suspected and documented chronic ischemic heart disease. This review will attempt to place the exercise electrocardiogram in perspective, and will limit discussion to clinical applications in patients with chronic ischemic heart disease. The reader is referred to several excellent reviews on the importance of physiologic exercise responses and on the use of the exercise test early after acute ischemic syndromes such as acute myocardial infarction or unstable angina (10–19).

Diagnostic Considerations

Historical perspective. In 1901, Einthoven introduced the string galvanometer to record the electrocardiogram, and
in 1908, published (20) the tracing of a patient who had ST segment depression after exercise. Although he did not recognize the clinical importance of this finding, electrocardiographic tracings were subsequently published (21–26), illustrating ischemic changes that occurred in patients during spontaneous episodes of angina and acute myocardial infarction and in experimental animal models shortly after coronary artery ligation. In 1928, Feil and Siegel (27) hypothesized that exercise-induced ST segment depression was caused by reduced coronary blood flow after observing these abnormalities after exercise in patients with chronic stable angina. Their data were confirmed by others, and improved quality of electrocardiographic recording devices and the ability to record precordial leads after the introduction of unipolar leads by Wilson in 1933 improved the sensitivity of the exercise test.

In 1941, twelve years after their initial publication describing the use of the 9 inch (22.86 cm) two-step test as a standard reproducible exercise protocol, Master et al. (28–30) published data on the use of the postexercise electrocardiogram as a means of detecting coronary insufficiency. Criteria for abnormality included depression of the RS-T segment of 0.5 mm or more below the isoelectric line or the new appearance of flat or inverted T waves. Arrhythmias or conduction disturbances were also considered an ischemic response. The specificity appeared excellent, and all 34 asymptomatic adults over 40 years had a negative double standard two-step test. The sensitivity in patients with angina pectoris was 39 and 67%, respectively, in patients who had a normal or abnormal rest electrocardiogram and was less in patients who had a previous myocardial infarction. The late 1940s were characterized by controversy over optimal diagnostic ST segment criteria (31–33).

In 1950, Wood et al. (32) noted that an abnormal exercise test could be produced in 90% of patients with angina pectoris who had a normal electrocardiogram at rest if a greater degree of exercise was performed than during the standard double two-step test. In their study, patients were encouraged to climb 84 steps from the physician’s consulting room to the top landing of the medical building. If the patients developed chest pain before reaching the top, they returned down the stairs and were reconnected to the electrocardiograph. The test was then repeated in-hospital under standardized conditions, climbing up and down a 12 inch (30.48 cm) step. The concept of silent myocardial ischemia was raised in their early report (32) when 26 patients developed a typical ischemic tracing after exercise but did not experience angina during the test.

Sensitivity and specificity. The next two decades were characterized by a trend toward the use of maximal symptom-limited exercise and improved recording techniques that permitted tracings to be acquired both during and after exercise (34,35). Multiple different electrocardiographic lead systems were tested, and in the early 1970s, exercise electrocardiographic results were compared with coronary angiographic findings (36–42). The sensitivity and specificity of different exercise electrocardiographic lead systems and ST segment criteria have been reviewed (42,43). The sensitivity of exercise-induced ST segment depression for obstructive coronary disease ranges from 56 to 81%, and specificity ranges from 72 to 96%. The sensitivity of ST segment criteria for one, two and three vessel coronary disease ranges from 40 to 84%, 63 to 91% and 79 to 100%, respectively. Correlation of exercise test data with angiographic findings reveals some of the limitations of the exercise test as a diagnostic method. In the 1970s, considerable controversy over the diagnostic usefulness of exercise testing was fueled by studies (44–47) of asymptomatic subjects with an abnormal exercise electrocardiogram who were referred for coronary angiography and found to have normal coronary arteries. Editorials such as “Whither the ST segment during exercise?” and “The exercise test in perspective” were published (48–52) in an attempt to clarify the use of diagnostic stress testing in different clinical patient populations.

Bayesian theory. The concept of a continuum of posttest risk based on the pretest risk of coronary disease and likelihood ratio (Bayesian theory) explains how conditional probability should be used to report exercise test results (53–61). The theoretical concepts of Bayesian theory have been confirmed in different clinical patient subsets stratified by character of chest pain (40,62–66).

Table 1 illustrates the post-test risk of obstructive coronary disease after a symptom-limited exercise test in patients without previous myocardial infarction stratified according to clinical presentation. The post-test risk of obstructive coronary disease ranges from 95% in men with typical angina who have an abnormal exercise electrocardiogram to less than 1% in asymptomatic women with a normal exercise electrocardiogram. Consideration must be given to age, sex, atherosclerotic risk factors, character of chest pain and other clinical variables in determining the pretest risk; likewise, the type of exercise electrocardiographic abnormalities (onset, depth, configuration of ST segment response, number of abnormal leads, duration of ischemic response) and physiologic variables (peak heart rate, peak treadmill time, and so on) must be used to determine the post-test disease probability for individual patients. Similar concepts apply to the exercise evaluation of the post-test risk for multivessel disease in survivors of myocardial infarction.

The predictivity of an abnormal test result for single or multivessel coronary disease is increased in older patients, in the presence of several atherosclerotic risk factors, in patients who have exercise-induced angina or a decrease in blood pressure during exercise and in patients with marked electrocardiographic abnormalities that appear early in exercise, in multiple leads and persist late into the recovery phase. Modifiers that decrease the risk of coronary
Table 1. Post-Test Risk of Obstructive Coronary Disease After a Symptom-Limited Exercise Test in Patients Without Previous Myocardial Infarction

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>ECG Abnormal*</th>
<th>Normal†</th>
<th>ECG Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical angina</td>
<td>95</td>
<td>50</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Probable angina</td>
<td>85</td>
<td>25</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>Nonspecific chest pain</td>
<td>40</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>30</td>
<td>5</td>
<td>5</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Horizontal or downsloping ST segment depression of 1 mm or more.
†Heart rate 85% or more of age-predicted maximum. All values are in percent. ECG = electrocardiogram.

Disease include younger age, achievement of higher exercise work loads and absence of exercise-induced J point depression.

**Drug effects and recording position.** The onset of ischemic ST segment depression, depth of ST segment depression at submaximal and maximal work loads and number of ischemic electrocardiographic leads is influenced by antianginal drug therapy (Fig. 1) (67–69). The influence of such therapy can mask the early onset of ST segment depression in patients with three vessel or left main coronary disease and obscure the diagnostic value of this sign as a marker for more severe coronary disease (70, 71).

The depth of ST segment depression and number of electrocardiographic leads with ischemic changes are accentuated in the supine versus upright position (72–74). Currie et al. (72) compared supine versus erect bicycle exercise in 43 patients with angina and no previous myocardial infarction. Exercise-induced ST segment depression of 1 mm or more occurred in 28 patients during erect exercise and in all 43 patients during supine exercise. The mean depth of ST segment depression was 1.3 mm in the upright position versus 2.6 mm in the supine position. The same investigators assessed supine exercise in 40 consecutive patients with chest pain and no coronary disease at angiography and found a specificity of 82% using the criterion of ST segment depression of 1 mm or more.

**Multivariate analysis.** Multivariate techniques have been used to quantify the incremental diagnostic yield of different noninvasive tests for the diagnosis and severity of coronary disease compared with estimates based on clinical variables alone (75–83). The data provide models whereby the post-test risk of disease can be estimated and provide another approach to determining the risk of coronary disease in different patient populations. In a study of 92 symptomatic women without previous myocardial infarction, Hung et al. (75) used a stepwise linear discriminant analysis of 41 clinical, exercise electrocardiographic, fluoroscopic and myocardial scintigraphic variables to determine which data were most predictive of coronary or multivessel disease. The analyses selected a reversible myocardial thallium defect, coronary calcification and character of chest pain syndrome as the variables most predictive of coronary disease, and cardiac fluoroscopic score, thallium score and extent of ST segment depression in 14 leads as the variables most predictive of multivessel disease. The same investigators (76) used multiple logistic regression analysis to assess the in-

![Figure 1](image-url)
incremental diagnostic yield of the addition of exercise electrocardiography, stress thallium scintigraphy and cardiac fluoroscopy to clinical data in predicting the likelihood of coronary and multivessel disease in 171 symptomatic men. The most significant variable predictive of coronary disease was an abnormal thallium scan; for multivessel disease, the amount of exercise performed was the most significant variable. Each noninvasive test incrementally improved predictive accuracy over clinical variables alone. However, the addition of cardiac fluoroscopy to the exercise electrocardiogram and thallium scan did not improve specificity. When the analyses were confined to multivessel disease as the end point, the addition of thallium scintigraphy to the exercise electrocardiogram only marginally improved specificity. The risk estimates determined by these and other multivariate models require prospective application to validate their predictive accuracy in other patient populations.

**Other Electrocardiographic Diagnostic Criteria**

**ST segment criteria.** Exercise-induced ST segment shifts remain the most widely used and accepted benchmark of myocardial ischemia. The criterion of horizontal or downsloping ST segment depression of 0.1 mV or more for 80 ms after the J point or ST segment elevation of 0.1 mV or more for 60 ms after the J point in non-Q wave leads appears to provide an optimal ratio of sensitivity to specificity. The criterion of a slow upsloping ST segment depressed by 0.2 mV at 80 ms after the J point is a useful criterion for myocardial ischemia when the pretest risk is high (84–86).

**R and Q wave amplitude criteria.** In early publications, Bonoris et al. (87,88) reported that an increase or no change in R wave amplitude in lead CM₃ immediately after exercise was suggestive of severe coronary artery disease and ischemic left ventricular dysfunction, whereas a decrease in R wave amplitude was considered a normal response occurring in patients without coronary artery disease. They reported a sensitivity of 63% and a specificity of 79% for R wave criteria compared with 48% and 59%, respectively, for ST segment criteria. Numerous later publications (89–92) have shown that R wave shifts are not a reliable predictor of coronary artery disease. Morales-Ballejo et al. (93) evaluated regression or progression of Q waves in lead CM₃ in 50 patients with coronary disease and 50 normal subjects to determine the presence or absence of coronary disease. They reported a sensitivity and specificity of 82% and 88%, respectively, for Q wave criteria compared with 52% and 74%, respectively, for standard ST segment criteria. Nohara et al. (94) assessed changes in exercise septal Q waves in lead Vₛ by single photon emission computed tomography in 107 patients. Of 18 patients who had regression of Q wave amplitude during exercise, 17 had a septal perfusion defect and all had left anterior descending coronary artery stenosis at angiography. Of 48 patients who had progression or no change of Q wave or a new Q wave during exercise in lead Vₛ, 90% did not have a septal perfusion defect; 56% of the 41 patients who had no Q wave at rest or during exercise had a left anterior descending coronary artery stenosis. These data support the findings of Morales-Ballejo et al. (93). R and Q wave amplitude changes are not widely used in the routine diagnostic assessment of patients with chest pain.

**U wave changes.** U waves in the left precordial leads of the 12 lead electrocardiogram may occur transiently in patients with coronary artery disease. In a study by Gerson et al. (95), 248 patients underwent exercise testing using leads CC₃ and aVL, 36 of whom had exercise-induced U wave inversion. Of 71 patients with left anterior descending or left main coronary artery stenosis of 50% or more and no previous history of infarction, 35% had U wave inversion compared with only 4% of 57 patients without left anterior descending or left main coronary artery disease and only 1% of 82 patients who had no coronary artery disease. In this study, U wave inversion was diagnosed if a discrete negative deflection within the TP segment relative to the PR segment occurred during or after exercise. Inverted U waves were not diagnosed if the exercise heart rate increased to a level such that the QT interval could not be accurately measured. The findings confirmed earlier observations (32) using a different technique and less sophisticated electrocardiographic techniques that transient U wave inversion is a useful marker of myocardial ischemia after exercise (96).

**Maximal ST/heart rate slope and quantitative treadmill exercise score.** Correlation of the maximal rate of progression of ST segment depression relative to increases in heart rate (maximal ST/heart rate slope) is reported to be a more precise indicator of myocardial ischemia than is ST segment depression alone (97–105). Elamin et al. (97) found 100% accuracy in stratifying 206 patients according to the presence and extent of coronary disease. Numerous other reports (98–102) published by the same team of investigators confirmed the initial results. Okin et al. (103) compared exercise electrocardiography with radionuclide cineangiography and coronary angiography in 35 patients with stable angina to assess the value of the ST/heart rate slope. Their data indicate that an ST/heart rate slope of 6.0 or more identified three vessel coronary disease with a sensitivity of 89% and a specificity of 88%. The exercise ST/heart rate slope was linearly related to the exercise change in left ventricular ejection fraction, although considerable scatter was present (103,104). Quyyumi et al. (105) assessed these criteria in 78 patients presenting with chest pain and found that the maximal ST segment/heart rate slope had a sensitivity of 90%, but a specificity of only 40%, and was not useful in predicting the extent of coronary disease. Clearly, additional studies by other groups of investigators are re-
quired to validate the use of ST segment/heart rate slope as a marker for the presence and severity of coronary disease.

The diagnostic accuracy of exercise electrocardiography can be improved by considering the depth of J point depression, ST segment slope, R wave amplitude, exercise duration and percent of maximal age-predicted heart rate (106–109). Hollenberg et al. (106) described a computer-derived treadmill exercise score using these variables derived from a Marquette case I system. The score integrates all ST amplitude and slope changes that occur during the test from the onset of exercise to the end of recovery and corrects the depth of the ST segment shift for R wave amplitude. The use of the treadmill score increased the sensitivity by 10 to 15% compared with conventional criteria in 59 patients who had obstructive coronary disease (106), and was useful in differentiating patients with three vessel or left main coronary artery disease from those with less severe coronary disease.

The degree of exercise-induced ST segment depression can be influenced by R wave amplitude, and perhaps should be normalized to a standard voltage (110–112). The precise "gain factor" correction for R wave amplitude requires further study. In the studies by Hollenberg et al. (111), the magnitude of ST segment depression was calibrated to a standard R wave amplitude of 12 mm in lead V5 and 8 mm in lead aVF. Hakki et al. (112) determined the influence of exercise R wave amplitude on ST segment depression in 81 patients with coronary disease. Among the 26 patients who had an exercise R wave amplitude of less than 11 mm in lead V5, only 8% had an abnormal exercise electrocardiogram versus 49% of the 55 patients who had an exercise R wave amplitude of 11 mm or more. The sensitivity of the exercise test was low in this study; 64% of the patients had inconclusive results. Exercise thallium scintigraphy increased the diagnostic sensitivity of the test in patients with a low R wave amplitude.

**Computerized Exercise Electrocardiography**

A discussion of computer-derived criteria to define exercise electrocardiographic markers of myocardial ischemia is beyond the scope of this review. The reader is referred to several excellent reviews on the subject (113–115). Most new exercise electrocardiographic equipment processes the data by computer to assist interpretation. The user should carefully understand the algorithms used to derive the computer-averaged tracings and should insist on display of raw data as well as computer-averaged data (Fig. 2).

Software programs are available that incorporate clinical and exercise test variables into a model to provide a post-test estimate of the risk of coronary and multivessel coronary artery disease and that predict the likelihood of subsequent coronary events. Diamond et al. (116) developed a CAD-ENZA program that incorporates age, sex, character of chest pain, atherosclerotic risk factors and other clinical and exercise test variables to provide a post-test risk estimate (± standard error) of coronary or multivessel disease. Although the diagnostic accuracy of this and other programs has been validated, additional research is required to validate the prognostic accuracy of these programs in other clinical centers where the patient referral patterns may be different (59,117). Clearly, in 1986, it is inappropriate to report a diagnostic stress test in terms of positive or negative.

**Supplementary noninvasive testing.** Supplementary noninvasive tests are often required to confirm or clarify the diagnosis of obstructive coronary disease. These ancillary techniques include cardiac fluoroscopy, exercise cardiokymography, exercise thallium imaging, exercise radionuclide

---

**Figure 2.** This unusual example of computer-averaged data (center panel) shows a stable baseline and 1.5 to 2.0 mm of horizontal downsloping ST segment depression; the raw data immediately before and after the averaged tracing show marked baseline drift and no significant ST segment depression. The raw exercise electrocardiographic data should always be displayed, as well as averaged complexes, before a final interpretation is made.
cineangiography and exercise two-dimensional echocardiography (118–139). The diagnostic importance of the techniques is greatest in patients who are asymptomatic or who have nonspecific chest pain and an abnormal exercise electrocardiogram, in patients with a high pretest risk of coronary disease and a normal exercise test and in patients who have baseline electrocardiographic abnormalities that render interpretation of the exercise electrocardiogram difficult. The radionuclide and echocardiographic tests provide data on global and regional left ventricular function that cannot be obtained from exercise electrocardiography alone.

Exercise Doppler echocardiographic techniques are a relatively new addition to supplementary noninvasive diagnostic exercise techniques (135–139). The method offers the opportunity to noninvasively determine stroke volume, cardiac output and peak ejection velocity. Bryg et al. (139) reported pulsed Doppler echocardiographic data in 20 normal subjects and 17 patients with coronary disease during upright treadmill exercise. In normal subjects, peak ejection velocity consistently increased more than 80% during exercise, nine patients with coronary disease had a blunted response, six patients had a decrease in peak ejection velocity with exercise and two patients had no change (Fig. 3).

Prognostic Considerations

Historical perspective. In 1953, Master et al. (33) reported 1 to 6 year follow-up data on 300 patients who underwent a double two-step test. The criterion for an abnormal test was ST segment depression of 0.5 mm or more or isoelectric-inverted T waves in leads I to III, V4 or V5 after exercise. Among the 150 patients who had an abnormal test, 24 had a subsequent myocardial infarction or unstable angina, and 10 died of cardiac causes. Among the 150 patients who had a negative test, only 1 had a myocardial infarction and none died; 94% of the original study group was symptomatic. In 1967, Robb and Marks (140) reported 10 year mortality results in 2,224 men, aged 40 to 65 years, who underwent a double two-step test. The criterion for abnormality was horizontal or downsloping ST segment depression of 0.1 mm or more in leads I, II, aVL, aVF and V4 to V6 after exercise. The 10 year mortality rate was 27% in patients with an abnormal test versus 6% in patients who had a normal test. The investigators noted that junctional ST segment depression and T wave inversion did not increase the risk of mortality, although increased depth of horizontal or downsloping ST segment depression resulted in an increased mortality gradient; 83% of the total study group were symptomatic.

Selected studies (141–146) that illustrate the prognostic significance of an abnormal exercise electrocardiogram in symptomatic patients are illustrated in Table 2. In the study by Ellestad et al. (141), profound ST segment depression of 2 mm or more, appearing at less than 3 minutes of the Ellestad protocol (4 MET), was associated with a 15% incidence rate of cardiac events per year versus only 4% per year when the ischemic abnormality was less marked or appeared at higher exercise work loads (≥ 8 MET). Podrid et al. (143) generated considerable controversy after publication of their study, which showed a low event rate in patients with “profound” ST segment depression during exercise. Their study differs from the other studies in that 42 of the 212 patients had no angina at the time of exercise testing, and the remaining patients may not have been very symptomatic; only 8% of the total number of patients subsequently underwent cardiac catheterization. The patients with heart failure or those receiving digitalis therapy were excluded. The strength of the study (143) is that the data are not taken from a consecutive series of patients who underwent cardiac catheterization, although the patient population appears to be highly selected.

Data from other studies (142,144,145) provide important information on risk group stratification based on exercise test results in patients with known coronary anatomy. In the study by Dagenais et al. (144), the annual mortality rate of patients with horizontal or downsloping ST segment depression of 2 mm or more in lead CM5 was significantly greater when patients were unable to exercise into stage III of the Bruce protocol. The risk was significantly less in patients with preserved exercise capacity. Chaitman et al. (147) stud-

Figure 3. Characteristic Doppler ultrasound tracing in a normal subject showing the typical increase in peak ejection velocity with exercise. Patients with coronary artery disease exhibited a blunted response. Pre and post = before and after exercise, respectively.
### Table 2. Prognostic Significance of an Abnormal Exercise Electrocardiogram in Symptomatic Subjects

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>Men (%)</th>
<th>Age (yr)</th>
<th>CAD (%)</th>
<th>Protocol</th>
<th>Criteria for Abnormality</th>
<th>Follow-up Duration</th>
<th>Prognosis (Based on ST Segment)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellestad</td>
<td>1975</td>
<td>2700</td>
<td>83</td>
<td>80%</td>
<td>NR</td>
<td>NR</td>
<td>H or D or U STD ≥ 1.5 mm; STE ≥ 1 mm</td>
<td>Annual mortality rate over 8 yr</td>
<td>Abnormal: 9.5%</td>
<td>Normal: 1.8%</td>
</tr>
<tr>
<td>and Wan (141)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNeer et al. (142)</td>
<td>1978</td>
<td>1472</td>
<td>NR</td>
<td>NR</td>
<td>40-60yr</td>
<td>Bruce</td>
<td>H or D STD ≥ 1 mm; STE ≥ 1 mm; 2 mm if STD at rest in 12 lead ECG</td>
<td>Annual mortality rate over 4 yr</td>
<td>+ ECG and Ex duration &lt; Bruce stage III: 9.3%</td>
<td>- ECG or Ex duration ≥ Bruce stage IV or max HR ≥ 160 Beats/min: 1.8%</td>
</tr>
<tr>
<td>Podrid et al. (143)</td>
<td>1982</td>
<td>212</td>
<td>100</td>
<td>57</td>
<td>Only 17 pts. had c. cath</td>
<td>Bruce</td>
<td>H or D STD ≥ 2 mm; U STD ≥ 2 mm at ST 80 in 12 lead ECG, reproducible on 2 tests</td>
<td>Annual mortality rate 59 mo</td>
<td>&lt; Bruce stage III = 2%/yr</td>
<td>&gt; Bruce stage III &amp; &lt; IV = 1.8%/yr</td>
</tr>
<tr>
<td>Dagenais et al. (144)</td>
<td>1982</td>
<td>107</td>
<td>92</td>
<td>51</td>
<td>96</td>
<td>Bruce</td>
<td>H or D STD ≥ 2 mm in lead CMs</td>
<td>Annual mortality rate over 5 yr</td>
<td>Bruce stage I = 9.6% (18); stage II = 5.4% (47); stage III = 2.8% (39); stage IV = 0 (3)</td>
<td>- ECG and Ex duration &lt; Bruce stage II: ≥ 5%</td>
</tr>
<tr>
<td>Weiner et al. (145)</td>
<td>1984</td>
<td>4083</td>
<td>77</td>
<td>89% &gt; 40 yr</td>
<td>67</td>
<td>Bruce</td>
<td>H or D STD ≥ 2 mm in 12 lead ECG</td>
<td>Annual mortality rate over 4 yr</td>
<td>- ECG and Ex duration ≥ Bruce stage III &lt; 1%</td>
<td>2%</td>
</tr>
<tr>
<td>Bonow et al. (146)</td>
<td>1984</td>
<td>117</td>
<td>91</td>
<td>48</td>
<td>100</td>
<td>Ergometer</td>
<td>H or D STD ≥ 2 mm in lead CMs, ML</td>
<td>Annual mortality rate over 4 yr</td>
<td>- ECG and Ex duration &lt; Bruce stage III &lt; 1%</td>
<td>0</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting; c. cath = cardiac catheterization; + ECG and - ECG = positive and negative electrocardiogram, respectively; EF = ejection fraction; Ex = exercise; FAI = functional aerobic impairment; H or D or U = horizontal or downsloping or upsloping, respectively; HR = heart rate; LMCD = left main coronary artery disease; LV = left ventricular; Max HR = maximal heart rate achieved; MI = myocardial infarction; NR = not reported; pts. = patients; STD = ST segment depression; STE = ST segment elevation; ST80 = 80 ms after the J point.
ied 83 symptomatic men without prior history of myocardial infarction who had exercise-induced horizontal or downsloping ST segment depression of 2 mm or more and who underwent cardiac fluoroscopy, thallium scintigraphy and coronary angiography. Among 38 patients unable to complete stage II of the Bruce exercise protocol, the post-test risk of coronary and multivessel disease was 0.97 and 0.88, respectively, and was not modified by the results of cardiac fluoroscopy or thallium scintigraphy. Among 45 patients with ST segment depression of 2 mm or more and peak work capacity up to or exceeding stage III of the Bruce protocol, the risk of coronary or multivessel disease was 0.76 and 0.44, respectively. The post-test risk of multivessel disease was increased from 0.44 to 0.82 when cardiac fluoroscopy and thallium scintigraphy were both abnormal, and was reduced to 0 when both supplemental tests were normal. These diagnostic data support the prognostic findings of Dagenais et al. (144) in patients who have a strong positive exercise electrocardiogram. The Coronary Artery Surgery Study (CASS) data reported by Weiner et al. (145) include the results of 572 patients with three vessel coronary disease who had a left ventricular contraction score of 5 to 9 (normal or mildly impaired left ventricular function); the mortality rate was 47% for 66 patients who were unable to complete Bruce stage I versus 0 for 10 patients who were able to enter Bruce stage V (Fig. 4). In another report from the CASS study, Weiner et al. (148) reported the 4 year mortality in patients with coronary disease (70% or greater stenosis) who had a negative exercise electrocardiogram and reached or exceeded Bruce stage III or 85% of the maximal age-predicted heart rate. The annual mortality rate was 1.5, 2.5 and 3.5% per year, respectively, for patients with one, two and three vessel coronary disease (Fig. 5).

The annual mortality rate in asymptomatic individuals or patients with mild angina appears to be lower than that in more symptomatic patients (143,146,149,150). Bonow et al. (146) reported exercise gated blood pool studies in 117 patients who underwent cardiac catheterization; patients with left main coronary artery disease or markedly impaired left ventricular function were excluded. In these mildly symptomatic patients, the mortality rate over a 5 year follow-up period was only 2% a year for patients with an abnormal exercise electrocardiogram versus 0 mortality in patients with a negative exercise electrocardiogram. Ryan et al. (149) reported exercise data from the CASS randomized trial of asymptomatic or mildly symptomatic patients. The presence of exertional ST segment depression was not associated with a significant increase in mortality, even when ST segment depression of 2 mm or more was observed. The data support the observations of Podrid et al. (143) for mildly symptomatic patients.

**Atypical chest pain.** The prognostic value of exercise electrocardiography in men and women with atypical chest pain was evaluated by Manca et al. (151). The incidence of myocardial infarction or sudden death was determined over an average 5.2 year follow-up after a bicycle ergometer stress test. In men with an abnormal exercise electrocardiogram (horizontal or downsloping ST segment depression ≥ 1 mm), the 5 year incidence rate of cardiac events was...
18.3% versus 1.9% in patients with a negative test. In women, the 5 year rate was 4.6% versus 0.3% when the test was negative. Hossack et al. (152) evaluated the incidence of hospitalization for angina, coronary bypass surgery, myocardial infarction and mortality in 551 men with atypical chest pain after a treadmill exercise test. The mean follow-up interval was 6.2 years. The presence of atherosclerotic risk factors increased the incidence of cardiac events, and exercise-induced ST segment depression, exercise duration and functional aerobic impairment were predictive of subsequent cardiac events. In men without atherosclerotic risk factors or abnormal exercise predictors, 96% were free of cardiac events compared with 76% of men with one or more of the abnormal exercise predictors (p < 0.001). The presence of atypical chest pain was not associated with cardiac mortality in men younger than 50 years of age.

Asymptomatic subjects. The prognostic importance of an abnormal exercise electrocardiogram in asymptomatic subjects is summarized in Table 3 (153–157). The protocol, criteria for abnormality and definition of an end point differ among studies. The risk ratio (probability of an event if the test is abnormal or normal) ranges from 3.2 to 4.14. In the study of McHenry et al. (156), an abnormal exercise electrocardiogram was associated with a 39% incidence rate of cardiac events over an average 6.3 year follow-up; 89% of the events were angina. A normal exercise electrocardiogram was associated with only a 5.3% incidence of events over the same time period; however, 73% of the events were either myocardial infarction or sudden cardiac death. In the Multiple Risk Factor Intervention Trial (MRFIT), a computer algorithm was used to determine an abnormal exercise ST segment response (157). Bruce et al. (155) studied 2,365 clinically healthy men who participated in the Seattle Heart Watch Study and who were followed up for an average 5.6 years after an exercise test. Subsequent primary coronary heart disease events, defined as a cardiac event requiring hospital admission, were more common in patients who had chest pain during maximal exertion, total exercise duration of less than 6 minutes with the Bruce protocol, failure to achieve 90% of age-predicted maximal heart rate and ischemic ST segment depression of 1 mm or more (Fig. 6). The data from asymptomatic men suggest that the prognostic information contained in the exercise test is of greatest value in patients who have atherosclerotic risk factors.

Conversion to an abnormal exercise electrocardiogram. In 1970, Doyle and Kinch (158) reported serial exercise data from 2,003 men who were exercised at least two times. The criteria for an abnormal post-exercise electrocardiogram were horizontal or downsloping ST segment depression of 1 mm or more, T wave changes consistent with "focal left ventricular epicardial ischemia" and paroxysmal left bundle branch block. Of 75 patients who developed an abnormal exercise test after initially normal results, 56% developed clinical manifestations of ischemic heart disease; the initial manifestation was angina pectoris in approximately half the subjects. In contrast to these results, McHenry et al. (156) found that conversion of a negative to positive exercise electrocardiogram did not substantially increase the risk of subsequent cardiac events compared with the risk of an initially abnormal test. In their study of the Indiana State Police Department, serial conversion to an abnormal exercise ST segment response in the absence of labile ST-T wave changes occurred in 38 subjects whose mean age was 51 years. The initial manifestation of coronary heart disease was angina in 10 of the 12 subjects who developed a cardiac event, a result similar to that obtained in the 23 subjects who had an initially abnormal exercise ST segment response. Of the 22 patients who had labile ST-T wave changes before exercise testing, none developed a subsequent cardiac event.

Exercise-induced ventricular arrhythmias. Exercise testing is often used to assess patients with serious ventricular arrhythmias (159–167). Occasionally, the exercise test will be the only test that will provoke a symptomatic underlying rhythm disturbance. The technique may be useful to identify patients at increased risk for sudden death and in selecting appropriate antiarrhythmic drugs. Young et al. (159) reported the complication rate of symptom-limited exercise in 263 patients with serious ventricular arrhythmias who underwent 1,377 maximal treadmill tests. The severity of the underlying arrhythmia disturbance is illustrated by the fact that 74% of the patients had a history of ventricular fibrillation or hemodynamically compromising ventricular tachycardia. During or immediately after the exercise test, 9% of the patients had either ventricular fibrillation, ventricular tachycardia or bradycardia that mandated immediate medical attention. However, there were no deaths, myocardial infarctions or lasting morbid events. The arrhythmia complication occurred at peak exercise in 57% of the 32 tests with cardiac events. Clearly, this type of patient should undergo exercise testing in a hospital environment with an indwelling intravenous catheter, a physician who knows the clinical history of the patient and a technician fully trained in cardiopulmonary resuscitation.

Prognosis of exercise-induced ventricular arrhythmias. The prognostic importance of an exercise-induced ventricular arrhythmia has to be interpreted in light of the clinical findings. In a presumably healthy subject, the appearance of simple or even complex induced ventricular arrhythmias does not predict subsequent cardiac events. Exercise-induced ventricular arrhythmias are common in healthy subjects as well as those ischemic heart disease, and the incidence increases with age and with greater exercise work loads. When an asymptomatic subject has exercise-induced sustained ventricular tachyarrhythmias that are reproducible, further cardiac evaluation is indicated to rule out a subclinical cardiomyopathy, myocarditis or silent ischemic heart disease (160–163).
## Table 3. Prognostic Significance of an Abnormal Exercise Electrocardiogram in Asymptomatic Subjects

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Age (yr)</th>
<th>Protocol</th>
<th>Criteria for Abnormality</th>
<th>% Abnormal Tests</th>
<th>Duration Follow-up (yr)</th>
<th>Prognosis (Based on ST Segment)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froelicher et al. (153)</td>
<td>1974</td>
<td>710</td>
<td>100</td>
<td>20 to 53</td>
<td>Balke or double two-step</td>
<td>H or D STD ≥ 1 mm in lead CC₃ or leads I, III, aVF, V₅, V₆; H or D STD ≥ 0.05 mm for double two-step</td>
<td>3.2</td>
<td>Average 6.3 yr</td>
<td>Abnormal: 8.6%</td>
</tr>
<tr>
<td>Allen et al. (154)</td>
<td>1980</td>
<td>888</td>
<td>65</td>
<td>NR</td>
<td>Ellestad</td>
<td>H or D STD ≥ 1 mm in any lead; 1.5 mm if abnormal STD at rest; in lead CM₃, V₃, or vertical bipolar</td>
<td>5</td>
<td>15</td>
<td>5 yr incidence</td>
</tr>
<tr>
<td>Bruce et al. (155)</td>
<td>1980</td>
<td>2,365</td>
<td>100</td>
<td>25 to 69</td>
<td>Bruce</td>
<td>H or D STD ≥ 1 mm persisting ≥ 1 min in recovery or ≥ 1 mm upsloping STD persisting ≥ 3 min in recovery in lead CB₂</td>
<td>11.1</td>
<td>5 yr probability event</td>
<td>Abnormal: 4.7%</td>
</tr>
<tr>
<td>McHenry et al. (156)</td>
<td>1984</td>
<td>916</td>
<td>100</td>
<td>27 to 55</td>
<td>Modified Balke</td>
<td>H or D STD ≥ 1 mm in lead CC₅</td>
<td>2.5</td>
<td>Average 6.3 yr</td>
<td>Abnormal: 39%*</td>
</tr>
<tr>
<td>MRFIT (157)</td>
<td>1985</td>
<td>6,205</td>
<td>100</td>
<td>35 to 57</td>
<td>Graded treadmill exercise</td>
<td>ST segment integral depressed 16 μVs in leads CS₃, aVL, aVF, V₅</td>
<td>12.2</td>
<td>5 yr</td>
<td>Cumulative mortality per 1,000 men; high risk asymptomatic population based on Framingham score; usual care group</td>
</tr>
</tbody>
</table>

SCD = sudden cardiac death; other abbreviations as in Table 2.
Figure 6. Of 2,635 clinically healthy men who participated in the Seattle Heart Watch Study, absence of clinical risk factors and less than two exercise (Exer.) risk predictors were associated with a very low incidence of primary cardiac events. In contrast, clinical risk factors associated with two or more exercise risk predictors were associated with a relatively high incidence of primary events. (Reproduced from Bruce et al. [155], with permission from the American Journal of Cardiology.)

In symptomatic patients with ischemic heart disease, complex ventricular arrhythmias are more common in patients with left ventricular contraction abnormalities and diffuse coronary disease. In a study of 620 patients with coronary artery disease reported by Califf et al. (164), the 3 year survival rate of patients with exercise-induced sustained ventricular tachyarrhythmias was 75% versus 83% in patients with exercise-induced isolated premature ventricular beats and 90% in patients without exercise-induced ventricular arrhythmias. The prognostic importance of the ventricular arrhythmias was reduced once cardiac catheterization data were considered. Nair et al. (165) and Weiner et al. (166) reported the prognostic importance of ventricular arrhythmias during or immediately after exercise in 280 and 86 patients, respectively. In both studies, the presence of exercise-induced ventricular arrhythmias was not associated with an increased cardiac mortality compared with that in patients without such arrhythmias. However, the number of patients with complex ventricular arrhythmias was small.

Sami et al. (167) studied 1,486 patients from the CASS registry who underwent a Bruce treadmill test and cardiac catheterization and were followed up for an average of 4.3 years. Exercise-induced ventricular arrhythmias were noted if premature ventricular beats were observed during the test but not in the 3 minute preexercise phase. A cardiac event was defined as death or readmission to the hospital for myocardial infarction, arrhythmia, unstable angina or heart failure. The 5 year incidence of events was not influenced by the presence of exercise-induced ventricular arrhythmias in patients with or without significant coronary artery disease. The presence of exercise-induced ventricular arrhythmias did not worsen prognosis, even in patients with limited exercise tolerance. In several of the reported studies, a detailed analysis of complex ventricular ectopic activity could not be performed, and the complete exercise tests were not recorded on tape; thus, significant ventricular arrhythmias may have been missed.

Clinical Implications

An exercise test result has to be interpreted in light of clinical findings. In most asymptomatic, apparently clinically healthy subjects, an abnormal exercise electrocardiogram does not indicate obstructive coronary disease, particularly when the electrocardiographic abnormalities appear at moderate or high exercise work loads. In several studies of asymptomatic individuals, the initial cardiac manifestation during follow-up after an abnormal exercise electrocardiogram is angina pectoris and not myocardial infarction or sudden cardiac death. Extrapolation from prognostic studies in symptomatic subjects indicates that the cardiac event rate in patients with known coronary disease is relatively low when patients are able to achieve a high exercise work load. The data indicate that coronary angiography may not be necessary in this type of mildly symptomatic patient. Marked electrocardiographic changes at low exercise work loads in an asymptomatic subject with a high clinical pretest risk requires further evaluation. Perhaps the greatest diagnostic value of exercise testing is in patients with atypical angina who have an intermediate pretest risk of coronary disease and in whom the presence or absence of marked electrocardiographic changes is helpful in formulating a decision for coronary angiography. In women with atypical angina, diagnostic exercise electrocardiography should be performed with supplemental diagnostic procedures as part of the initial diagnostic assessment of chest pain.

The main indications for performing an exercise test in patients with typical angina are to establish functional capacity, determine a baseline for repeat measurements in subsequent years, assess an antianginal drug therapy and revascularization procedures and have a prognostic risk estimate that can be used to formulate decisions about indications for coronary angiography and revascularization procedures. Coronary artery bypass grafting has been shown to improve survival in patients with left main coronary artery disease and in mildly symptomatic patients with three vessel coronary disease and impaired left ventricular function (168–171). The European Coronary Surgery Study (172) reported improved survival after coronary bypass surgery in patients with three vessel coronary disease and normal left ventricular function and in patients with two vessel coronary disease and 75% or more narrowing in the proximal segment of the left anterior descending coronary artery. Thus, the presence of marked exercise electrocardiographic
abnormalities in men and women with typical angina, which are often associated with more severe coronary artery disease and an adverse prognosis, should mandate early coronary angiography and a revascularization procedure if clinically indicated. The prognostic data from exercise testing and natural history studies of symptomatic patients with less severe obstructive coronary artery disease suggest that in selected patients, coronary angiography can be deferred when symptoms are mild and the electrocardiographic abnormalities appear at moderate to high exercise work loads.

Many new diagnostic electrocardiographic criteria have been proposed in recent years, and new supplemental diagnostic procedures have been introduced. The role of exercise testing in the diagnostic and prognostic assessment of patients with suspected or proved ischemic heart disease has been established after more than 50 years of investigation. The new electrocardiographic criteria and supplemental diagnostic procedures require additional study to determine their role and cost-effectiveness in the exercise evaluation of patients with ischemic heart disease.

References


60. Epstein SE. Implications of probability analysis on the strategy used for noninvasive detection of coronary artery disease. Role of single or combined use of exercise electrocardiographic testing, radionuclide cineangiography and myocardial perfusion imaging. Am J Cardiol 1980;46:491–500.


77. Kansal S, Roitman D, Bradley EL, Sheffield LT. Enhanced evaluation of treadmill tests by means of scoring based on multivariate


98. Mary DASG, Elamin MS, Smith DR, Linden RJ. Use of submaximal ST segment/heart rate relation during maximal exercise testing to predict severity of coronary artery disease (abstr). Br Heart J 1981;45:342P.


155. Bruce RA, DeRouen TA, Hossack KF, Blake B, Hofer V. Value of
maximal exercise tests in risk assessment of primary coronary heart

156. McHenry PL, O’Donnell J, Morris SN, Jordan JJ. The abnormal
exercise electrocardiogram in apparently healthy men: a predictor of
angina pectoris as an initial coronary event during long-term follow­

157. MRFIT. Exercise electrocardiogram and coronary heart disease mor­
tality in the Multiple Risk Factor Intervention Trial. Am J Cardiol

158. Doyle JT, Kinch SH. The prognosis of an abnormal electrocar­

159. Young DZ, Lampert S, Graboys TB, Lown B. Safety of maximal
exercise testing in patients at high risk for ventricular arrhythmia.

160. Woelfel A, Foster JR, Simpson RJ, Gettes LS. Reproducibility and
treatment of exercise-induced ventricular tachycardia. Am J Cardiol

Am Coll Cardiol 1985;5:9B–12B.

162. Woelfel A, Foster JR, McAllister RG, Simpson RJ, Gettes LS. Efficacy of verapamil in exercise-induced ventricular tachycardia.

163. Pratt CM, Yepsen SC, Bloom MGK, Taylor AA, Young JB, Qui­
nones MA. Evaluation of metoprolol in suppressing complex ven­

164. Califf RM, McKinnis RA, McNeer JF, et al. Prognostic value of
ventricular arrhythmias associated with treadmill exercise testing in
patients studied with cardiac catheterization for suspected ischemic

significance of exercise-induced premature ventricular complexes in
men and women: a four year follow-up. J Am Coll Cardiol

166. Weiner DA, Levine SR, Klein MD, Ryan TJ. Ventricular arrhythmias
during exercise testing: mechanism, response to coronary bypass

Significance of exercise-induced ventricular arrhythmia in stable
 coronary artery disease: a Coronary Artery Surgery Study project.

bypass surgery on survival patterns in subsets of patients with left

169. Detre KM, Takaro T, Hultgren H, Peduzzi P, and the study partic­
ipants. Long-term mortality and morbidity results of the Veterans
Administration randomized trial of coronary artery bypass surgery.

Study (CASS): a randomized trial of coronary bypass surgery. Eight
years follow-up and survival in patients with reduced ejection frac­

171. Passamani E, Davis KB, Gillespie MJ, et al. A randomized trial of

Survival, myocardial infarction, and employment status in a pro­
spective randomized study of coronary bypass surgery. Circulation