Contemporary Reviews in Cardiovascular Medicine

Exercise Electrocardiogram Testing
Beyond the ST Segment

Paul Kligfield, MD; Michael S. Lauer, MD

Exercise testing remains the most widely accessible and relatively inexpensive method for initial evaluation of suspected coronary disease and for evaluation of its severity. \(^1\)–\(^3\) Clinical usefulness has been limited, however, by poor sensitivity of standard ST-segment depression criteria for assessment of anatomic and functional coronary disease severity and for prediction of risk. \(^1\)–\(^2\),\(^4\)–\(^6\) Recent data make it clear that symptomatic obstructive plaques that typically result in exercise-mediated ischemia may be less relevant to infarction and sudden death than less obstructive unstable plaques. \(^7\) These limitations mandate a rethinking of the exercise ECG along 2 distinct lines: First, is it possible to improve the diagnostic value of the exercise ECG? Second, separate from its ability to diagnose obstructive coronary artery lesions, can the exercise test be used as a prognostic tool that can encourage effective prevention of premature deaths or coronary events? Both goals take us beyond the ST segment.

Beyond the ST Segment: What Are We Looking for?

Reversible ST-segment depression is the characteristic finding associated with exercise-induced, demand-driven ischemia in patients with significant coronary obstruction but no flow limitation at rest. This process differs from the flow-limited acute coronary syndromes because exercise-related ischemia is generally limited to the subendocardium and is proportional to increases in myocardial oxygen demand. Ventricular waveforms of the ECG can be related to the net uncanceled transmural gradients between endocardial and epicardial myocardium, as extrapolated from the work of Holland and Brooks, among others. \(^5\)–\(^10\) Accordingly, isoelectric TQ and ST segments in normal and in nonischemic patients can be related to comparable resting membrane and action potential plateau voltages in endocardial and epicardial action potentials. During exercise, progressive ischemia results in changing endocardial action potentials during both diastole and systole. Less negative endocardial cell resting membrane potential leads to current flow across the ischemic boundary during diastole, leading to elevation of the TQ segment on the ECG. Lower endocardial plateau voltage leads to current flow during systole, leading to ST-segment depression. \(^11\)

These combined diastolic and systolic effects of subendocardial ischemia produce ST-segment depression. The magnitude of ST depression during ischemia is related to spatial and nonspatial factors. \(^12\) The spatial factor is roughly the area of ischemic myocardium; the larger the involved area, the greater is the ST depression. The first nonspatial factor is the physiological severity of ischemia within the affected myocardium, which becomes progressively greater during exercise and is largely responsible for the changing amount of ST depression during the test. An additional nonspatial factor that may affect ST-segment depression during exercise-induced ischemia is changing intraventricular conductance. \(^9\),\(^12\)

It is immediately apparent from these considerations with regard to mechanisms that many conditions can confound the sensitivity and specificity of the ECG for the detection of coronary disease and for the anatomic, functional, and prognostic predictive value of the ST-segment response. These confounders include the presence of nonobstructive but vulnerable lesions in the coronary arteries, subthreshold nonspatial severity of ischemia with inadequate effort tolerance or blunted heart rate response to exercise, any cause of high endocardial wall stress that can limit subendocardial flow reserve, and electrolyte and drug effects on the action potentials, as well as ST-segment cancellation from opposingly oriented discontinuous areas of ischemia, among others. \(^6\),\(^11\),\(^13\) These considerations and the past 50 years of experience have taught us that we need to go beyond the ST segment.

Before alternative exercise test methods are considered, it is important to acknowledge inherent limitations in diagnostic accuracy of any noninvasive test. Alternative methods of imaging during ischemia, such as echocardiography and perfusion scanning, reach beyond the ST segment and have inherent limitations; a detailed discussion of these tests extends beyond the scope of this report.

Tests should be evaluated in the population to which they will be applied. However, most of the diagnostic literature is based on patient samples in which all subjects had both the diagnostic test and a coronary angiogram. \(^6\) Because patients

From the Division of Cardiology, Weill Medical College of Cornell University and the Cornell Center of the New York–Presbyterian Hospital, New York, NY (P.K.); and the Departments of Cardiovascular Medicine, Quantitative Health Sciences, and Epidemiology and Biostatistics, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio (M.S.L.).

Reprint requests to Michael S. Lauer, MD, Desk JJ40, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195. E-mail lauerm@ccf.org

(Circulation. 2006;114:2070–2082.)

© 2006 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.105.561944

2070
who did not undergo angiography were not considered, the reported test accuracy is inaccurate. This phenomenon of “referral bias,” also known as “verification bias” or “workup bias,” occurs because the decision to perform the gold standard test (eg, angiography) is heavily influenced by the results of the diagnostic test and physicians’ faith in them. Verification bias inflates estimated sensitivity and deflates estimated specificity.

Test sensitivity is also dependent on the study population and generally increases with the severity of disease. The standard exercise test tends to correctly identify patients with high-grade proximal multivessel or left main coronary disease but to incorrectly miss patients with less severe obstruction. Test performance is dependent on the admixture of disease in the population, making comparison of test performance difficult across broadly defined groups. Too much effort has been expended in comparing one test with another. We are not necessarily looking for one ECG feature that will improve identification of disease but perhaps a logical combination of findings.

Another important interpretive limitation of the exercise test has been its dependence on coronary angiography as the diagnostic gold standard. Prognostically important coronary disease may be present in the absence of hemodynamically obstructive lesions. Under conditions of stress, inadequate coronary vasodilatation or paradoxical constriction may generate ischemia without any requirement for fixed resting stenoses. Thus, the prognostic value of a test for a clinical outcome may differ strikingly from its sensitivity and specificity characteristics for the presence of underlying obstructive disease.

**Beyond the ST Segment: Diagnostic Value of the ECG for Detection of Ischemia or Obstructive Coronary Artery Disease**

Dependence on a discrete ST-segment threshold for the definition of exercise-induced myocardial ischemia reduces the sensitivity of the standard exercise test. As a single continuous variable, the magnitude of measured ST depression at peak exercise limits test performance to that defined by the intrinsic reciprocity of sensitivity and specificity. Improvement in test performance of the exercise ECG cannot occur without the incorporation of additional information beyond the ST segment. As a corollary, new criteria and combinations of findings should be capable of altering the performance of any diagnostic test.

To go beyond limitations of the ST segment, it is necessary to consider the effects of exercise-related, demand-induced ischemia on other features that can be extracted from the ECG. Heart rate normally increases through exercise in proportion to myocardial oxygen demand and is therefore related to the onset and severity of ischemia. Even if not contained within a single cardiac cycle, heart rate is an intrinsic part of the ECG and can be measured easily. Other ischemic ECG findings include changes in QRS duration, QRS amplitudes, QT intervals, observed QT dispersion, and subintervals of repolarization, such as the duration from the peak to the end of the T wave.

**Heart Rate Adjustment of ST Depression**

ST depression during exercise-induced ischemia is dependent not only on the presence of coronary obstruction but also on the increase in excess myocardial oxygen demand as workload increases. This suggests a physiologically sensible principle: Because ST segment depression changes throughout the course of exercise, it must reflect more than just coronary obstruction. Because changes in heart rate are related to changes in myocardial oxygen demand, adjustment of ST depression for changes in myocardial oxygen demand related to heart rate is therefore physiologically logical.

Two methods of heart rate adjustment of ST-segment depression during exercise have evolved (Figure 1). Methodologies of the linear regression–based ST segment/heart rate (ST/HR) slope and the simpler ST/HR index have been detailed elsewhere. Much of the improved sensitivity results from correct classification of threshold levels of upsloping ST-segment depression that is classified as “equivocal” because upsloping depression is common in normal subjects. Heart rate adjustment of subthreshold ST depression <0.1 mV also results in correct classification of “false-negative” tests, but this will only occur when ST-segment measurement is precise. With high sensitivity but lower specificity, these methods serve as a reasonable screen for identification of 3-vessel or left main coronary artery disease and are more accurate than standard criteria for identifying extensive obstruction as defined by high Duke jeopardy or Gensini scores or by larger reductions in exercise ejection fraction during exercise radionuclide cineangiography.

Watanabe et al found useful predictive value of the ST/HR index during supine bicycle testing for identification of 3-vessel disease and significant correlation with the Gensini score. More recently, favorable reports from Lee et al and Hsu et al have supported the ST/HR index for improved detection of disease. The ST/HR index alone and a summation of index values have also been demonstrated to
have enhanced value for prediction of restenosis after percutaneous transluminal coronary angioplasty.53,44 Hamasaki et al45 recently developed a criterion of subtracting the ST/HR index from the ST/HR slope, which has allowed for detection of coronary artery disease in patients on digoxin. However, improved performance with the use of heart rate–adjusted measures of ST depression has not been found in all studies, perhaps in part because of methodological and population differences.23,46–49

**QRS Duration**

Sympathetic stimulation increases conduction velocity, whereas ischemia tends to decrease conduction velocity by slowing the rapid upstroke (phase 0) of the ventricular action potential. It has been postulated that differences in QRS duration from rest to exercise might serve as a marker of ischemia. A subtle prolongation of QRS duration during exercise was demonstrated by Ahnve et al50 in 1986. Modest exercise QRS shortening in normal subjects was found by Michaelides et al.51 The magnitude of change in these studies was small, in the range of 3 ms of shortening in normal subjects and 6 to 8 ms of lengthening in coronary disease patients. Berntsen et al52 were able to associate more marked exercise-induced QRS prolongation, in the range of 15 ms, with increased risk for subsequent ischemia-related ventricular tachycardia. Computer-based optical scanning for more precise measurement of QRS duration during exercise testing was introduced by Cantor et al53 and was found to outperform standard ST-segment criteria for identification of disease in women54,55 and for the detection of post–percutaneous transluminal coronary angioplasty restenosis.56 These methods are amenable to computer-based implementation in digital ECGs.

**QRS Amplitudes**

QRS amplitudes have been examined in several ways as markers for ischemia. According to the “Brody hypothesis,” other things being equal, the R-wave amplitude recorded by the surface ECG should be proportional to chamber size and the ischemic dilatation of the left ventricle may thereby be recognized. Bonoris et al57 demonstrated in 1978 that failure of R-wave amplitude to decrease during exercise was associated with modestly useful sensitivity and specificity. Adjustment for R-wave amplitude differences improved the performance of the Hollenberg treadmill score.58,59 Other studies have been less positive, including the finding of opposite directional changes.60 Detrano et al32 found that R-wave behavior with exercise alone had limited performance but that there was some diagnostic advantage in normalizing ST depression for R-wave amplitude. Although Ellestad et al61 found some value in R-wave normalization, this was limited to patients with extreme amplitudes.

Another algorithm, the Athens QRS score, has had increasing support in recent reports.62,63 The score examines net amplitudes in leads aVF and V1 by subtracting Q and S amplitudes from the R wave in each lead at rest and during exercise and then subtracting the exercise result from the rest result in each lead. Values for these rest-exercise differences in each lead are then added to produce the resulting score. Initial findings suggested that the score was inversely related to the anatomic extent of disease, always associated with disease when negative, and independent of the presence or absence of ST depression.62 It was also found to be inversely related to the extent of ischemic wall motion abnormalities63 and to the magnitude of exercise-induced, handgrip-induced, and dipyridamole-induced perfusion abnormalities.64,65 Subsequent studies indicated value of the Athens score for the detection of restenosis and for ischemia after bypass surgery.56 Koide et al66 demonstrated that the Athens QRS score added complementary diagnostic information to ST-segment depression.

High-frequency components of the QRS complex that are not usually represented in the routine ECG tracing, between 150 and 250 Hz, have been shown to decrease in the presence of acute ischemia.68 An initial report found that reduction of high-frequency forces during exercise may have useful sensitivity and specificity for the detection of coronary disease.69

**QT Interval and T-Wave Subintervals**

Evaluation of the QT interval during exercise is subject to a number of methodological problems. Noise and baseline drift increase the difficulty of determination of the end of the low-frequency T wave. Fusion of the end of the T wave with the subsequent P wave as heart rates rise further obscures the end of repolarization. QT-interval restitution is not instantaneous with change in cycle length but depends on the rate and direction of changing cycle length, which varies throughout exercise. Moreover, the rate of QT-change with exercise is different in men and in women.70,71 Limitations notwithstanding, a number of studies have suggested that lengthening of the rate-corrected QT interval with exercise identifies myocardial ischemia,72–74 particularly in patients with exercise-related ventricular arrhythmias.75

An immediately confounding difficulty with QTc, however, is the generally different peak exercise heart rates that are found in patients with and without disease and the general inapplicability of traditional rate correction algorithms within the exercise environment. Lax et al76 demonstrated that Bazett-corrected QTc interval prolongation (the measured QT divided by the square root of the RR interval) was only minimally greater in patients with coronary disease than in normal subjects when measured at corresponding subthreshold heart rates. The small differences present in QTc at peak exercise were also present at rest, arguing against important diagnostic value for the QTc during exercise testing.

On the other hand, differences between normal subjects and patients with coronary disease in a marker of precordial QT dispersion in the study by Lax et al76 diverged throughout exercise at all heart rates and provided information that was complementary to standard measures of ST-segment depression. QT dispersion can be defined simply as the difference between the longest and shortest measured QT in any lead or, alternatively, as a standard deviation of all measured QT intervals in the ECG. A number of studies have indicated useful predictive value of QT dispersion for the identification of disease and ischemic contractile dysfunction during exercise57,77–81 and after adenosine infusion.82 Although considerable controversy exists about the relationship of QT dispersion to heterogeneity of repolarization, it is clearly dependent...
on underlying T-wave morphology, which might be expected to be sensitive to exercise-induced ischemia. Further examination of T-wave subintervals during exercise is warranted, such as the T peak to T end duration.83,84 Other T-wave measures that have been found to have prognostic value in the resting ECG, such as principal component analysis,85,86 require clarification in the exercise test environment.

Recovery Phase Methods

Because postexercise ST-depression resolution is asymmetrical with respect to heart rate in patients with myocardial ischemia, the pattern of ST-segment change in relation to heart rate during the recovery phase of exercise also has diagnostic value.23,87–90 Data can be examined qualitatively as the simple rate-recovery loop,91 with findings from the first minute of recovery, when patients with ischemia generally have greater ST-segment depression than was present at the corresponding heart rate during exercise before peak effort (Figure 2). In contrast to standard ST-depression criteria and heart rate–adjusted criteria derived purely from exercise phase data, the sensitivity of the rate-recovery loop appears to be relatively independent of the extent of disease. The rate-recovery loop has been found to be more useful than ST-depression criteria for the identification of restenosis after angioplasty.92

Recovery phase and exercise phase ST behavior were incorporated by Hollenberg et al98,99 into a treadmill exercise score that is adjusted for heart rate. A number of more recent studies have confirmed the diagnostic value of combining exercise and recovery phase ST-segment data in the heart rate domain. A relatively simple quantification of the rate-recovery loop involves calculation of the ST-segment “deficit” between recovery phase ST depression at 3.5 minutes and the ST depression at the corresponding heart rate during exercise.89,93 ST/HR hysteresis, as developed by Lehtinen et al88,94,95 integrates the area of ST-segment depression with respect to heart rate that is included in the exercise and recovery loop over the heart rate range included in the first 3 minutes of recovery. This integral is then divided by the heart rate difference (ie, the maximum heart rate during exercise minus the minimum heart rate during recovery) of the integration interval to normalize the result with respect to the postexercise heart rate decline.

In one large study, comparison of receiver operating characteristic curves demonstrated that performance of ST/HR hysteresis exceeded that of the ST/HR index and standard test criteria for the detection of coronary artery disease.88 A recent evaluation by Svensburgh et al96 has addressed the effect on test performance of the exact range of heart rates included in the rate-recovery area calculation, noting that a large percentage of the loop needs to be considered to optimize diagnose, especially in women. Bigi et al96 examined the entire rate-recovery loop by defining a stress-recovery index as the difference in areas under the full exercise and recovery phase ST/HR plots. The stress-recovery index has been found to be more accurate than other standard ST segment– and heart rate–adjusted test methods for the identification of anatomically extensive disease after myocardial infarction,96 for the prediction of mortality after myocardial infarction,97 and for the prediction of all-cause mortality in hypertensive patients with chest pain.98

Thus, combination of exercise and recovery phase ST-segment data as an area of the ST/HR loop appears to be the most accurate and predictive of the current heart rate–adjusted methods in routine exercise testing. Recovery phase behavior of other potential ECG markers of ischemia, such as QRS duration, Athens QRS score, and QT-interval derivatives, also deserve careful attention.90,96–98 As shown by Koide et al97 for complementary performance of ST depression and Athens QRS score, it is reasonable to predict that combinations of these methods should be capable of improving the performance of the exercise ECG for the detection of those patients who have demand-induced ischemia. Accordingly, we believe that continued development and multicenter evaluation of the applied value and limitations of these newer methods are warranted.

Application in Current Clinical Practice

We recommend the incorporation of the simple ST/HR index into routine exercise test evaluation, and we believe that other measurements and combinations of measurements require further evaluation and/or technical implementation before application becomes practical.19 Reasons for use of the ST/HR index include simplicity of calculation, improvement in test sensitivity by resolution of otherwise “equivocal” test responses, and demonstrated prognostic value in Framingham men and women and in higher-risk Multiple Risk Factor Intervention Trial (MRFIT) participants.18,99–101 The ST/HR index is derived by dividing the maximal additional change in ST-segment depression at end exercise, measured in microvolts (where 1.0 mm at standard gain = 100 μV) at a constant 60 ms after the J point,46 by the corresponding change in heart rate from upright control. Additional ST depression compared with upright control is determined only by deviation below the isoelectric line, with excursion from any ST elevation to baseline not included.23 This requires no automated computer algorithm for calculation as needed for routine application of the more complex ST/HR slope and ST/HR hysteresis deter-
minations, but precision of measurement contributes to test accuracy, particularly when subthreshold ST depression is present. In practice, averaging of 3 successive complexes is effective. Alternatively, computer-averaged ST-depression values can be accurate to 0.1 mm (10 μV), but these always require visual verification. Values of the ST/HR index >1.6 μV/bpm are abnormal.

Although the linear regression–based ST/HR slope and ST/HR hysteresis have been implemented in some computer-based algorithms, these are not yet ready for widespread implementation. This is due to technical calculation issues and other methodological factors. Clinicians who find value in the simple ST/HR index may wish to explore the ST/HR slope and hysteresis in greater detail. Implementation of QRS duration, QRS score, and high-frequency QRS findings awaits confirmatory studies and practical application of automated signal-averaged QRS measurements in routine exercise ECG recording equipment. QRS amplitude change, as well as QTc, has been of disappointing value when used alone; whether these will find a role in expanded algorithms remains to be seen. Newer algorithms examining QT hysteresis and T-wave shape require further evaluation and are not yet ready for practice.

Beyond the ST Segment: Prognostic Value of the Exercise ECG

Prediction of future coronary events and mortality can be separated from the identification of obstructive disease as an important use of the exercise ECG. We will focus on methods that are intrinsic to the information contained in the exercise test, such as effort tolerance, and within the ECG signal itself, including heart rate changes and ventricular arrhythmias. Methods with demonstrated prognostic value include simple heart rate adjustment of ST-segment depression, measurements of functional capacity, chronotropic competence and incompetence, heart rate recovery, and frequent ventricular ectopy during recovery (Table 1). Exercise test scores, which incorporate clinical and demographic risk factors not based on the exercise test, will be examined briefly.

Functional Capacity

It may be argued that the most important prognostic marker obtained by the exercise test is functional capacity or the amount of work completed before exhaustion. Extensive literature in asymptomatic cohorts has demonstrated that functional capacity is a powerful independent predictor of all-cause and cardiovascular mortality. More recently, functional capacity has been studied within a clinical context. For example, a study of >3000 patients undergoing stress testing with single-photon emission computed tomography nuclear myocardial perfusion imaging demonstrated that functional capacity was at least as strong a predictor as perfusion defects for prediction of all-cause death. Similarly, a study of an angiographic cohort showed that functional capacity was a stronger predictor of death than angiographic severity of coronary disease and ST depression. When functional capacity and the presence or absence of angiographic coronary disease were considered together, only functional capacity predicted death (Figure 3).

Despite its enormous prognostic power, the use of functional capacity in routine clinical care is problematic because of a lack of standardization. Functional capacity is strongly related to age and gender. Thus, an estimated functional capacity of 7 metabolic equivalents (METs) (where 1 metabolic equivalent is ~3.5 mL/kg per minute of oxygen consumption) in a 40-year-old man would be prognostically more concerning than the same value in a 60-year-old woman. Functional capacity tends to decrease with age and for any given age is higher in healthy men than in healthy women. Some groups have characterized functional capacity as being abnormal if <5 METs in women or <7 METs in men. Others have considered functional capacity to be impaired if within the lowest quartile of any given age or gender group. These approaches do not capture the continuous nature of functional capacity and also may not be easily transportable from one population to another.

Efforts have been made to derive nomograms for accurate characterization of functional capacity (Figure 4). A nomogram for predicted functional capacity in men has long been available. In the past year, nomograms for women have been described and validated as predictive of mortality in symptomatic populations. It has been suggested that a functional capacity of <85% of predicted would characterize substantial prognostic risk, but this has only been validated in women.

Chronotropic Response to Exercise

Normally, heart rate increases during exercise. As previously described, the initial increase in heart rate early in exercise is thought to be caused by a central withdrawal of parasympathetic inhibition as well as an increase in sympathetic tone. Later there is a further increase in central nervous system sympathetic stimulation as well as in levels of circulating catecholamines. The decrease in parasympathetic tone, along with the increase in sympathetic tone, results in increased stimulation of the sinus node and increased heart rate.

Chronotropic incompetence is an inability of the heart rate to increase normally with exercise. In a classic article by Colucci et al, patients with increasing severity of heart failure had a progressively impaired chronotropic response perhaps due to decreased sensitivity of the sinus node to sympathetic stimulation. Investigations in population-based and clinical cohorts demonstrated that an impaired chronotropic response is predictive of cardiac events and all-cause mortality. A major challenge in using chronotropic response in clinical exercise testing is determining how best to characterize it. The simplest approach is to report peak heart rate and change in heart rate with exercise. However, peak heart rate is at least moderately related to age as peak heart rate decreases with increasing age. Therefore, efforts have been made to normalize chronotropic response for age.

A relatively straightforward way of accomplishing this is to report the percentage of age-based predicted maximal heart rate. A number of regression formulas have been derived, the classic one being 220 minus age in years; thus, a 40-year-old person would have an estimated maximal-predicted heart rate.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Populations Studied</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST/HR index</td>
<td>Maximum change in ST depression/change in HR: (Peak Exercise—Upright Control ST)/(Peak Exercise—Upright Control HR)</td>
<td>Catheterized patients, clinical CAD without catheterization, asymptomatic high-risk men and low-risk men and women</td>
<td>Increases sensitivity for the detection of CAD and predicts mortality and cardiovascular events</td>
</tr>
<tr>
<td>ST/HR slope</td>
<td>Greatest statistically significant slope by linear regression relating ST depression to HR during exercise</td>
<td>Catheterized patients, clinical CAD without catheterization, clinically normal men and women</td>
<td>Increases sensitivity for the detection of CAD and for identification of anatomically and functionally severe CAD when markedly abnormal</td>
</tr>
<tr>
<td>Estimated functional capacity in METs</td>
<td>Based on protocol and exercise time</td>
<td>Symptomatic and asymptomatic men and women</td>
<td>Strongly predictive of mortality and cardiovascular events (although prognostic value of &lt;85% of predicted has only been validated in women)</td>
</tr>
<tr>
<td>Chronotropic response</td>
<td>Proportion of HR reserve use calculated as (Peak HR—Resting HR)/(220—Age—Resting HR)</td>
<td>Symptomatic and asymptomatic men and women</td>
<td>Predictive of mortality and cardiovascular events; limited evidence regarding usefulness with β-blockers</td>
</tr>
<tr>
<td>HR recovery</td>
<td>Difference between HR at peak exercise and HR 1 or 2 min later</td>
<td>Symptomatic and asymptomatic men and women</td>
<td>Predictive of mortality, cardiovascular events, and sudden cardiac death</td>
</tr>
<tr>
<td>Ventricular ectopy during recovery</td>
<td>Frequent ventricular ectopics (&gt;7 bpm), couplets, bigeminy, trigeminy, ventricular tachycardia, or fibrillation</td>
<td>Symptomatic and asymptomatic men and women</td>
<td>Uncommon but predictive of all-cause mortality</td>
</tr>
<tr>
<td>Duke treadmill score</td>
<td>Minutes (Bruce Protocol)—5×ST-Segment Deviation—4×Angina Score</td>
<td>Symptomatic and asymptomatic men and women</td>
<td>Predictive of cardiovascular mortality and all-cause mortality</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; HR, heart rate.
of 180 bpm. An inability to achieve at least 85% of age-predicted maximum heart rate has been considered chronotropic incompetence and predicts an increased mortality risk.114

Still, there is concern that this mode of age correction does not fully account for other confounding factors, namely, functional capacity and resting heart rate. An alternative approach has been to consider the proportion of heart rate reserve used at peak exercise.24,114 At baseline, a patient has a predicted heart rate reserve, which is the difference between age-predicted maximal and resting heart rates. During exercise, heart rate would increase to a certain amount. The difference between the heart rate at peak exercise and the heart rate at rest is divided by the heart rate reserve to determine the proportion of heart rate reserve used. Some have termed this value the chronotropic index,114 whereas others have simply described it as the proportion of heart rate reserve used during exercise.116 Recent studies have suggested that this measure is a better predictor of mortality than the more traditional percentage of age-predicted heart rate.116

Some laboratories are therefore considering a value of proportional heart rate reserved used of 80% to constitute prognostically important chronotropic incompetence.114,116

Heart Rate Recovery
During the first few minutes after exercise, heart rate declines, a phenomenon closely related to autonomic function.120–123 The decrease in heart rate during the first 30 seconds to 1 minute after exercise is primarily related to parasympathetic reactivation.120 Because of the extensive literature relating parasympathetic nervous system function and dysfunction to mortality,124,125 it had been hypothesized that an attenuated heart rate recovery after exercise predicts increased risk of death.87

Since the initial reports linking heart rate recovery to mortality were first published ≈6 years ago,87,126 there have been many confirmatory reports. An attenuated heart rate recovery has been shown to predict mortality in asympto-
atic subjects,\textsuperscript{127} patients undergoing coronary angiography,\textsuperscript{128} patients undergoing stress echocardiography,\textsuperscript{129} and patients undergoing nuclear myocardial perfusion imaging.\textsuperscript{87} Heart rate recovery predicts death independent of confounders, including left ventricular systolic function,\textsuperscript{129} functional capacity,\textsuperscript{87,126} and angiographic severity of coronary disease.\textsuperscript{128}

A major challenge in the use of heart rate recovery in routine clinical exercise testing has been how best to characterize it.\textsuperscript{130,131} Heart rate recovery is strongly dependent on the type of recovery protocol used. The first reports of heart rate recovery were based on patients who underwent an upright cool-down protocol with a slow walk during the first 2 minutes after exercise.\textsuperscript{87,126} A heart rate recovery value of $\leq 12$ bpm was identified as a best-value cut point.\textsuperscript{87} However, in patients undergoing different kinds of protocols, such as those undergoing stress echocardiography or those sitting down after exercise,\textsuperscript{131} heart rate recovery values tend to be higher. Thus, for patients undergoing stress echocardiography, an abnormal value of $\leq 18$ bpm has been reported,\textsuperscript{129} whereas in patients undergoing a more classic type of recovery protocol, the abnormal reported value has been $<22$ bpm over 2 minutes of recovery.\textsuperscript{131}

It is not entirely clear why patients with an impaired heart rate recovery have an increased risk.\textsuperscript{123} Some have suggested a predisposition to fatal arrhythmias and sudden cardiac death.\textsuperscript{132} It has been shown that the presence of frequent ventricular ectopy during recovery is itself a predictor of death and is a better predictor of death than ventricular ectopy during exercise.\textsuperscript{133} In addition, a recent report of asymptomatic subjects suggested that an attenuated heart rate recovery was a stronger predictor of sudden cardiac death than other modes of death.\textsuperscript{134}

Both heart rate recovery\textsuperscript{128,131} and chronotropic response\textsuperscript{135} have been shown to be associated with worsening degrees of angiographic coronary disease, but these associations are weak. It is not clear whether heart rate measures predict responses to revascularization. One recent observational study found that heart rate recovery could be used to identify patients with ischemia who might benefit from revascularization.\textsuperscript{136} Of note, ischemic patients with an impaired heart rate recovery were at very high risk of long-term mortality and did not gain a mortality benefit from revascularization. In contrast, those patients with a normal heart rate recovery seem to gain a substantial survival benefit. Another critical question is whether heart rate recovery is modifiable. Reports supporting this possibility have shown improvements in heart rate recovery after formal exercise training of cardiac patients.\textsuperscript{137,138}

Exercise-Induced Angina

Because suspected angina pectoris is a common clinical symptom among patients referred for exercise testing, it is not surprising that angina sometimes occurs during or immediately after the test. Angina, whether test-limiting or not, was found to be predictive of cardiac mortality in the original cohort on which the Duke treadmill score was derived.\textsuperscript{139} However, a number of other cohort studies have failed to find an independent predictive value of exercise-related angina once other measures, like functional capacity, were accounted for.\textsuperscript{126,140–142}

Heart Rate–Adjusted Measures of ST Depression

The simplicity of the simple ST/HR index calculation has made it retrospectively applicable to the evaluation of risk in large population studies. Among asymptomatic low-risk men and women in Framingham, the simple ST/HR index significantly concentrated risk of cardiac events (defined as sudden death, myocardial infarction, or new-onset angina pectoris), especially in women, by $>3$-fold during a 4-year follow-up.\textsuperscript{99} Standard ST depression alone did not significantly concentrate risk. Among asymptomatic but higher-risk men in the MRFIT population, the ST/HR index but not standard exercise test criteria concentrated the risk of cardiac death in the usual care group by 4- to 5-fold.\textsuperscript{101} An abnormal ST/HR index identified a group of MRFIT men in whom therapy aimed at reducing coronary risk factors was associated with a $>50\%$ reduction of subsequent cardiac death.\textsuperscript{100}

Incorporation of Non-ECG Information Into Exercise Test Scores

The prognostic value of the exercise test has been improved by the use of scores that combine ECG data with clinical descriptors of risk.\textsuperscript{143} Among the simplest and most popular of these is the Duke Treadmill Score, which adds exercise duration and the presence and test-limiting severity of angina to ST-segment depression (Table 1).\textsuperscript{139,144,145} The score also stratifies coronary artery disease subgroups,\textsuperscript{146} and its predictive value appears to be maintained in patients with abnormal repolarization on the resting ECG\textsuperscript{143} but may be reduced in the elderly.\textsuperscript{147} More recent scores have incorporated increasingly larger numbers of clinically derived risk factors to the exercise findings, such as age, sex, lipid levels, smoking history, and hypertension.\textsuperscript{143,148,149}

Therapeutic Implications

Like any other clinical test, exercise testing would be of little value if its results do not lead to changes in management. The current premise underlying the use of exercise testing is that by identifying patients likely to have coronary disease and/or likely to be at increased risk for premature events, aggressive preventive interventions can be initiated appropriately.\textsuperscript{150} Although intuitive, there is surprisingly little evidence demonstrating that outcome is improved as a result of obtaining data from an exercise test. Some observational data of exercise testing combined with imaging suggest that test data may effectively guide appropriate selection of patients for revascularization.\textsuperscript{136,151} However, we lack randomized trial data in which the strategy of interest is whether or not to obtain an exercise test (with or without imaging) at all, as opposed to empiric aggressive medical therapy and/or coronary angiography. Randomized trials of diagnostic tests have been performed in other fields of interest, like breast cancer screening\textsuperscript{152} and detection and management of abdominal aortic aneurysms.\textsuperscript{153} Elsewhere, we have called for a randomized trial of exercise testing as a screening modality in asymptomatic adults believed to be at risk for coronary disease.\textsuperscript{154} Although we recognize that it may be impractical,
TABLE 2. Elements of Conclusion Section of a Modern Exercise Test Report

<table>
<thead>
<tr>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/positive/equivocal standard ST-segment response to exercise.</td>
</tr>
<tr>
<td>The ST/HR index of ≤1.6 μV/bpm is consistent with the absence of</td>
</tr>
<tr>
<td>obstructive coronary disease and makes anatomically, functionally, and</td>
</tr>
<tr>
<td>prognostically important coronary disease unlikely; the ST/HR index &gt;1.6</td>
</tr>
<tr>
<td>μV/bpm is consistent with the presence of obstructive coronary disease</td>
</tr>
<tr>
<td>and predicts increased cardiovascular risk.</td>
</tr>
<tr>
<td>The estimated functional capacity of XX METs predicts high/low risk of</td>
</tr>
<tr>
<td>all-cause mortality.</td>
</tr>
<tr>
<td>The Duke treadmill score of X predicts a cardiac mortality of X% per year</td>
</tr>
<tr>
<td>over the next 5 years. This implies a (low/intermediate/high) risk.</td>
</tr>
<tr>
<td>The chronotropic response index of 0.6X predicts an increased/decreased</td>
</tr>
<tr>
<td>risk of death compared with the Duke treadmill score. For patients not on</td>
</tr>
<tr>
<td>β-blockers, a value of &lt;0.80 raises concerns; for patients on β-blockers,</td>
</tr>
<tr>
<td>a value ≥0.62 is abnormal.</td>
</tr>
<tr>
<td>The heart rate recovery of XX bpm further predicts an increased/decreased</td>
</tr>
<tr>
<td>risk of death.</td>
</tr>
<tr>
<td>The presence/absence of frequent ventricular ectopy during recovery</td>
</tr>
<tr>
<td>further increases/decreases predicted risk of death.</td>
</tr>
</tbody>
</table>

given current accepted practice patterns, to institute such a trial, it is still worth noting that despite decades of research we do not have unequivocal evidence showing that exercise testing or any other noninvasive cardiac test improves clinical outcomes.

It is not known whether key measurements, such as functional capacity and heart rate recovery, provide markers that, if modified, improve prognosis. These markers may predict risk because they reflect a number of important pathophysiological pathways, including inflammation155 and autonomic imbalance.120 Although prediction of risk is clinically valuable, these measures would arguably be of greater clinical interest if prognosis could be directly modified on the basis of these findings. Although definitive trials are lacking, meta-analyses of the cardiac rehabilitation literature suggest that interventions to improve functional capacity may reduce long-term mortality.156,157

Conclusions

Despite the well-known limitations of the standard exercise ECG for diagnosing obstructive coronary disease, the exercise test continues to have substantial diagnostic and prognostic value when measures beyond simple ST-segment depression are considered. Diagnostic capability may be improved by heart rate adjustment of the ST depression and measurement of QRS duration and amplitude, QT- and T-wave changes, and ST-recovery loops and hysteresis. The enormous prognostic value of exercise testing is based primarily on measures of functional capacity, chronotropic response, heart rate recovery, and ventricular ectopy during recovery.

Recent discoveries relating to the diagnostic and prognostic value of exercise testing can transform the standard report. Instead of describing a test as “normal” or “abnormal,” typically centered on ST-segment changes, the report should include the major prognostic findings along with their implications. Thus, for a patient with interpretable ST segments, the conclusion section of the report might list the elements shown in Table 2.

The modern exercise laboratory should no longer content itself as serving its function by merely reporting visually estimated ST-segment changes. Exercise testing in the 21st century has moved beyond the ST segment.

Sources of Funding

Dr Lauer received support from the National Heart, Lung, and Blood Institute (grants R01 HL-66004, R01 HL-072771, and P50 HL-77101).

Disclosures

Dr Kligfield reports occasional consulting and equipment support from GE Healthcare, Philips Medical Systems, and Mortara Instrument. Dr Lauer reports no conflicts.

References


Key Words: electrocardiography | exercise | heart rate | physiology | prognosis
Exercise Electrocardiogram Testing: Beyond the ST Segment
Paul Kligfield and Michael S. Lauer

Circulation. 2006;114:2070-2082
doi: 10.1161/CIRCULATIONAHA.105.561944
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/19/2070

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

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

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