Principles of simple heart rate adjustment of ST segment depression during exercise electrocardiography

Paul Kligfield

Weill Cornell Medical College, Cornell Center of The New York Presbyterian Hospital, New York, USA

Abstract

Compared with standard test criteria, simple heart rate (HR) adjustment of ST depression during exercise electrocardiography can improve the identification and assessment of underlying coronary artery disease. Since heart rate during exercise drives progressive ST segment depression in the presence of coronary obstruction that limits flow reserve, the ST/HR index controls for the increasing metabolic severity of ischemia that accompanies exercise. Improvement of exercise test sensitivity with the ST/HR index results from reclassification of otherwise "equivocal" and even "negative" test responses, including increased identification of one and two-vessel disease in men and in women. In addition, in population studies of low and moderate risk subjects, the ST/HR index can increase the prognostic value of the exercise electrocardiogram for prediction of cardiac risk and mortality. (Cardiol J 2008; 15: 194–200)

Key words: exercise, exercise testing, exercise electrocardiogram

The exercise electrocardiogram (ECG) remains the most widely available and easily accessible test for the evaluation of patients with suspected coronary artery disease [1, 2]. Under different circumstances, the exercise ECG can be used to confirm a clinical diagnosis of myocardial ischemia, to evaluate the anatomic and functional severity of coronary disease, to assess exercise capacity and to provide prognostic information regarding risk in symptomatic subjects. The exercise ECG has been the subject of a number of recent reviews, some of which emphasize the increasing value of examining functional aspects of exercise performance [3–5]. By way of contrast, this discussion will focus on the traditional ST segment component of the exercise test, with emphasis on the principles that underlie simple heart rate (HR) adjustment of the ST segment to produce a more useful test criterion known as the simple ST/HR index [4, 6].

What is wrong with traditional ST segment criteria during the exercise ECG? As we all know

from practice, poor sensitivity of the ECG for the detection of ischemia is a major diagnostic weakness and the critical limitation of the test. In standard meta-analysis, 1.0 mm (0.1 mV) of horizontal or downward-sloping ST depression has a sensitivity of only 68% for the detection of coronary obstruction [7]. Although sensitivity can be increased with less rigorous definitions of test positivity, such as including upward-sloping ST depression, this occurs only with an unacceptable loss of test specificity. In other words, with ST segment depression as the only criterion, fewer false negative exercise ECGs must result in more false positive tests. No change in test partition can represent test improvement under these conditions.

Think about the dynamic changes that occur during exercise in a patient with typically positive ST segment depression during an exercise test. At rest, there is generally no ST segment depression. Somewhere in the course of progressive exercise, there will be 0.5 mm of ST depression, which, if the

test were stopped, would constitute a "negative" exercise ECG response. As the patient continues to exercise at a higher workload on the treadmill or on the bicycle, ST segment depression progressively increases to become 1.0 mm below the baseline, compared with only 0.5 mm earlier in the test. At this point, assuming the depression is horizontal or downward sloping, the test would be considered "positive". Imagine that the patient continues, with or without chest pain, to exercise to an even greater workload. At that later time point there might be 2.0 mm of ST depression and we might call the test "very positive" or "markedly positive." This leads to a major interpretive problem with the standard exercise test. The problem is that the definition of the test outcome in this situation is dependent on when the test is stopped, not on the pathophysiology of coronary artery disease.

It can be argued that the problem with the simple exercise ECG is our dependence on the magnitude of ST segment depression for the definition of the test outcome [4, 6, 8, 9]. In reality, despite broad average correlation, the magnitude of ST segment depression alone at peak exercise does not work very well for the identification of coronary artery disease or for the assessment of its anatomic severity [10]. What is more, it is hardly a strong marker for the presence of vulnerable plaque, the instability of which leads to the clinical variants of acute coronary syndrome, including myocardial infarction and unstable angina. We need to extend our definition of the ECG response to exercise beyond simple determination of the magnitude of peak exercise ST depression alone.

How can this be done in a practical and physiologically sensible way? From a physiological perspective based on solid angle theory (a model that seeks to explain the magnitude of ECG voltages recorded on the surface of the body), ST segment depression can be related to two major variables [11, 12]. The first variable is the spatial extent of ischemia, in effect, the size of the anatomic area of myocardium that is affected by ischemia. This will be greater with proximal than with distal coronary obstruction within single vessels, and greater with multivessel disease than with single vessel disease if proximity of the obstructions are comparable. The second variable is the non-spatial extent of ischemia, in effect, the metabolic severity of ischemia within the individual myocardial cells involved in the area distal to flow limiting coronary obstructions. Metabolic severity at the cellular level will vary with the extent to which myocardial oxygen demand in the ischemic myocardium exceeds the available supply,
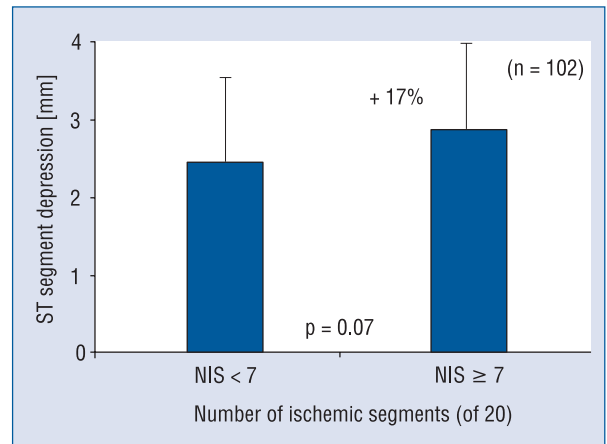

Figure 1. Relation between ST segment depression and the number of ischemic segments during exercise perfusion scanning. Although average ST depression increases with anatomically more extensive ischemia, the 17% difference does not reach statistical significance in 102 patients with coronary disease. Adapted from data in Am J Cardiol, 2005; 96: 1356–1360.

as toxic metabolites increase with increasing muscle cell work in the presence of limited blood flow. It correlates with the local loss of membrane voltage that accompanies myocardial cell ischemia, producing a voltage gradient across the ischemic boundary. Both variables interact to produce the ST segment depression recorded by the ECG, but neither factor alone can account for the ST depression that occurs during exercise testing.

It is clear that, in general, the anatomical extent of ischemia can be related to the magnitude of ST segment depression [2, 6, 7, 10, 13]. Patients with single vessel disease have, on average, less ST segment depression during exercise than patients with two-vessel coronary disease. Similarly, patients with two-vessel disease, again on average, have less ST depression than patients with three-vessel or left main coronary disease. But the range of ST depression is quite variable within each anatomic distribution, and there is considerable overlap. It is not uncommon for an individual patient with three-vessel disease to have less ST depression than another individual patient with only two-vessel or even single-vessel disease.

The effect of the anatomical extent of ischemia on ST segment depression can be examined in exercise nuclear perfusion studies, as shown in Figure 1. This figure relates the magnitude of ST depression in 102 patients with coronary artery disease to the number of reversibly ischemic segments, grouped as less than 7, or greater than or equal to 7 segments,
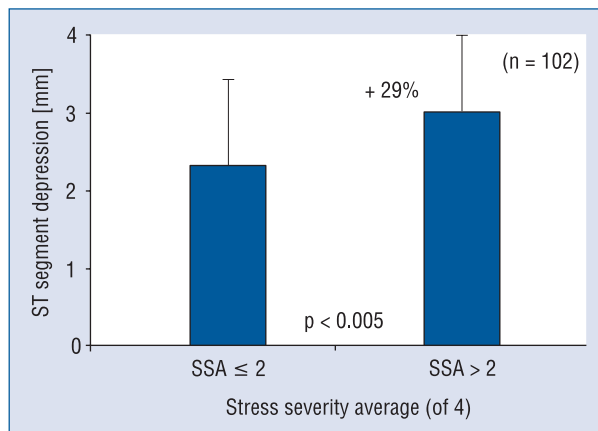
Figure 2. Relation between ST segment depression and the average severity of ischemia during exercise perfusion scanning, as measured by an average severity score (overall stress severity score divided by the number of ischemic segments, based on a 0 to 4 ischemic severity scale for each ischemic segment). Higher stress severity average is associated with a 29% increase in ST segment depression. Adapted from data in Am J Cardiol, 2005; 96: 1356–1360.

of a total left ventricular area of 20 segments [10]. Note that while mean ST depression is greater in the group with more ischemic segments during exercise, this 17% increase does not reach statistical significance because of the large standard deviations and the modest number of patients. Statistical significance would be found for these differences in larger groups, but the point is that the overlap of ST segment depression values between groups is considerable because the number of ischemic segments, a spatial factor related to anatomical location of obstructions, does not alone determine exercise ECG findings.

The corresponding effect of the metabolic severity of ischemia can be seen in Figure 2. This shows the relation of ST segment depression in groups separated by average stress severity scores, which represents the average magnitude of relative ischemia within involved segments (on a 1 to 4 scale for each segment, with 4 most severe). This is only a very vague approximation of the voltage drop due to ischemia across an ischemic boundary, but it is a usefully illustrative approximation. With groups separated according to stress severity scores of less than or equal to 2, or greater than 2, it can be seen that there is a 29% increase in ST segment depression in patients with greater severity of average ischemia within segments [10]. This difference is statistically significant and gre-

ater than the effect of increased area of ischemia in this same population. These observations suggest that the metabolic severity of ischemia is at least as important, and may be more important, than the area of ischemia alone for the production of exercise-induced ST segment depression.

This is consistent with routine observations that are available to everyone who performs exercise ECGs. If we re-examine the typical course of a positive standard exercise ECG, there is usually no ST segment depression at rest or during very early exercise. As progressive exercise by treadmill or bicycle increases through programmed stages, at some point there will be 0.5 mm of ST segment depression, and then (because we have defined this as a positive test example) with further workload there will be 1.0 mm of ST depression. Indeed, if the patient remains comfortable and workload increases to an even higher stage, at some point there may be 1.5 mm, 2.0 mm or even more ST depression. What is happening here? Surely, the anatomic extent of coronary disease is not increasing from none at the start of the test, to some during the middle of the test and to a large amount with increasing effort at the end of the test. Rather, what is happening is that the metabolic severity of ischemia is increasing after the point in progressive exercise in which myocardial work exceeds the coronary flow reserve allowed by the anatomic obstructions [4, 6]. There is no ischemia at rest, moderately severe metabolic ischemia in the middle of the test and more severe ischemia at the end of the test, at peak effort, when myocardial oxygen demand is at its greatest.

Because ST segment depression during exercise is driven largely by the progressively increasing exercise workload, 1.0 mm of ST segment depression (an empiric partition, rooted in the past) is not a physiologically stable marker for the identification of the presence or the extent of coronary artery obstruction. As a consequence of its workload dependence, peak exercise ST depression is the wrong variable for the evaluation of coronary disease. To derive more useful information about coronary artery disease during ischemia, ST segment depression during the course of exercise needs to be adjusted in some way for the dynamic factors that cause it to change during progressive treadmill or bicycle workload. The relevant dynamic factor during exercise can be shown to change HR, not exercise duration or time.

We have seen that ST segment depression during exercise-induced ischemia can be directly related both to the anatomical extent of disease and

to the severity of ischemia induced by a changing myocardial workload, as predicted by the solid angle model [11, 12]. In effect, these principles can be expressed as a simple equation, where:

manifest ischemia (ST depression) = extent of CAD × severity of ischemia,

where the severity of ischemia reflects the voltage change across an ischemic boundary due to the metabolic consequences of exercise. To compensate for the changing severity of ischemia during effort, we can apply a very important observation from physiological experiments that are now over 20 years old. Working with an isolated perfused myocardial preparation, Mirvis et al. [14, 15] demonstrated that the voltage decrease across an ischemic boundary could be linearly related to the rate at which the heart cells were being paced: the faster the HR, the greater the voltage decrease in the ischemic cells.

Accordingly, changing ST depression during exercise-induced ischemia can be related to the product of the extent of disease and changing HR. Heart rate change is known to be important in exercise testing [13]. Remember that HR at higher levels of exercise is linearly related to myocardial oxygen demand [14, 16]. Once an ischemic threshold is reached, changing heart rate drives changing ST depression, independent of but still proportional to the extent of disease [6]. As a result, HR is a more relevant physiological parameter for the analysis of ischemia than is exercise time or exercise duration [4, 6, 9, 12]. If we use the exercise ECG to make inferences about the presence and extent of coronary artery disease, we can rework the equation above to produce a more useful test outcome:

extent of disease = changing ST depression/ /changing heart rate.

Two major methods have evolved to adjust changing ST segment depression for corresponding HR changes during exercise [6, 17]. These are schematically illustrated in Figure 3, in which exercise HR is shown on the horizontal (X) axis, and ST segment depression is shown as a positive change on the vertical (Y) axis (in this arrangement, ST depression, even though negative in value, is plotted as a "positive" finding). The first method is the ST/HR slope, originally developed in nearly simultaneous studies in England and in Hungary nearly 30 years ago [18–20]. The ST/HR slope seeks to
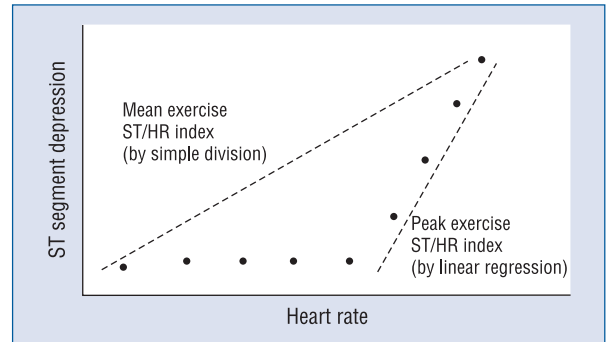

Figure 3. The ST/HR slope and the simple ST/HR index. While the ST/HR slope is calculated by linear regression from data during changing ST depression at the end of exercise, the ST/HR index is derived from simple division of the overall change in ST segment depression by the overall change in heart rate during the entire test.

calculate the steepest statistically significant slope of linear regression at the end of exercise in any lead. This method is cumbersome and time-consuming, but it is easily automated [21]. For the purpose of this discussion, we will limit attention to the simpler second method, which is known as the ST/HR index. The ST/HR index is obtained simply by dividing the overall additional change in ST depression from control to peak exercise in the lead with the maximum ST depression by the overall change in HR during the course of exercise [4, 6]. For both the ST/HR slope and ST/HR index methods, ST depression is measured 60 ms after the j-point, regardless of the upward-sloping, horizontal, or downward-sloping nature of the ST segment depression (to anticipate, inclusion of upward-sloping ST depression in these calculations offers the possibility of improving both test sensitivity and test specificity, if otherwise "equivocal" tests with only upward-sloping ST depression are correctly classified by the new algorithm). Leads aVR, aVL, and V1 are excluded because ST depression with T-wave inversion in these leads in normal subjects is common. For practicality, ST depression is measured in microvolts (μV), where 1 mm or 0.1 mV of ST depression is equal to 100 μV. When dividing overall ST depression by the change in heart rate, which is usually less than 120 beats per minute (bpm), the use of μV measurement allows the resulting ST/HR index to fall into single digit units between 0.0 and 6.0, depending on the individual values.

Normal values for the ST/HR index were derived from exercise test findings in a large number of clinically normal subjects. By the method of
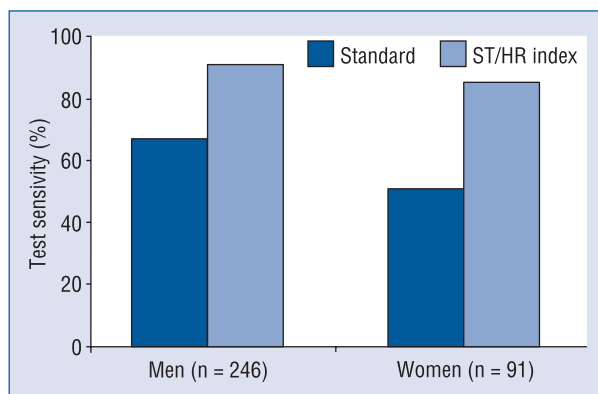
Figure 4. Identification of coronary artery disease in men and in women by standard exercise test criteria (navy bars) and by the simple ST/HR index (blue bars). Sensitivity of the exercise test increases with the use of the ST/HR index in both men and women, but the proportionate increase is greater in women, in whom the standard test performs poorly. Adapted from data in Circulation, 1995; 92: 1209–1216.

percentile estimation, 95% of normal subjects had ST/HR index values of less than 1.6 μV/bpm [17]. What this normal value means is that the maximal "normal" ST depression that is found in 95% of normal subjects is related to heart rate. By dimensional analysis, this indicates that up to 160 μV of ST depression (1.6 mm) may be found in normal subjects exercising to a peak heart rate that is 100 bpm greater than that of the control, or up to 100 μV (1.0 mm) in normal subjects when the peak heart rate change is 62 bpm or more.

When applied in a large number of patients with catheterization proven coronary artery disease and also in patients with clinically stable angina without cardiomyopathy, the ST/HR index partition of 1.6 μV/bpm improved the sensitivity of the exercise ECG from 68% with standard ECG ST segment depression criteria to 90%, with no significant fall in test specificity [17]. Interestingly, improvement in test sensitivity was even greater in women than in men with the use of the ST/HR index (Fig. 4), due in part to the generally poor test sensitivity of the standard exercise ECG in women [22]. At matched test specificities of 96% for both standard exercise ECG and ST/HR index methods, sensitivity of the ST/HR index for coronary disease rose from 70% to over 90% in men and from only just over 50% to over 80% in women. Reasons for the improved sensitivity of the ST/HR index include identification of considerably more patients with only single and double vessel coronary artery disease

(the standard test is actually reasonably sensitive for three-vessel and left main coronary disease, although the ST/HR index is still better), a high prevalence of correct reclassification of patients and subjects with otherwise "equivocal" standard test responses by the ST/HR index partition of 1.6 μV/bpm, and even identification of some patients with truly negative standard test responses [6].

A number of studies from around the world have provided support for the improved diagnostic value of simple HR adjustment of ST segment depression during exercise testing [23–29], but other studies have not found any advantage [30, 31]. Readers are invited to examine the value of the ST/HR index method in their own practice. It is simple and requires no complex analysis tools, just simple division of overall change in maximum ST depression by the heart rate change during exercise. In doing this simple calculation, several technical issues should be borne in mind:

— First, ST segment depression should be measured at 60 ms after the j-point in the lead with maximum end-exercise ST depression relative to resting control. Other measurement points are not as accurate in separating patients with disease from normal subjects with similar ST depression.

— Second, use of bipolar CM5 (a manubrium to V5 electrode pairing), improves test sensitivity, even when using the 12 standard ECG leads.

— Third, for determination of additional ST depression, only change in the ST segment level below baseline is considered, and all rest or early exercise ST elevation above baseline is ignored; for example, a subject with 2.0 mm of ST elevation at baseline, perhaps due to "early repolarization", who has 1.0 mm of ST depression at peak exercise will have ST depression of 1.0 mm (100 μV), not 3.0 mm (300 μV).

— Fourth, precision of ST segment measurement matters, since it forms the numerator of the ST/HR index. In particular, it is critical that ST depression less than 1.0 mm be measured carefully and not taken as 0.0; this would mean that all values of the ST/HR index would be 0.0 as a result; this can occur inadvertently in retrospective application of the method to test findings that are not reviewed for actual subthreshold values of ST depression.

— Finally, the change in ST depression considers all ST depression, even when upward sloping, in the calculation of the ST/HR index; one of the strengths of the method is the correct classification of these otherwise "equivocal" test

responses that ordinarily do not reliably distinguish between patients with coronary disease and normal subjects with exercise-related upward-sloping ST depression.

In addition to the detection and assessment of the anatomical and functional extent of obstructive coronary artery disease, an important application of the exercise ECG is the stratification of future coronary risk, which is not necessarily the same process as identification of the disease. The value of the simple ST/HR index in comparison with standard exercise ECG criteria in two large population studies is therefore of interest. In a four-year follow-up evaluation of cardiac event rates in over 3,000 initially asymptomatic adults in a cohort of the Framingham Study, a statistically significant relative risk of 3.1 was found for a positive ST/HR index (absolute risk 5.4 *vs*. 1.7), but not for the standard ST segment response alone [32]. Of note, risk of new cardiac events was concentrated more strongly by the ST/HR index in women than in men (relative risk 5.4 in women, 2.6 in men). In a slightly higher risk, but still asymptomatic, population of nearly 6,000 men in the usual care arm of the MrFIT trial, the relative risk of cardiac mortality during a seven-year follow-up was a statistically significant 4.1 for subjects with a positive ST/HR index (absolute risk 5.4 *vs*. 1.3), but not for the standard exercise ECG [33, 34].

Additional advantages are found with HR correction of ST segment depression by means of linear regression, which is beyond the scope of this introduction [6, 17, 35, 36]. Also beyond the scope of this introduction are methods that have examined the heart rate domain behaviour of ST segments during the recovery phase of exercise, as well as more recent methods that have combined exercise and recovery phase ST segment hysteresis behaviour with respect to heart rate [37, 38]. Each of these methods require computer based assistance for accuracy of calculation, but they can be recommended for consideration for those whose experience with the ST/HR index suggests that improvement of exercise ECG performance is indeed possible.

In summary, simple heart rate adjustment of ST depression during exercise compensates for the increasing metabolic severity of ischemia to clarify the underlying extent of disease. Improvement of exercise test sensitivity with the ST/HR index results from the reclassification of otherwise "equivocal" and even "negative" test responses, including increased identification of one and two-vessel disease in men and women. And perhaps most importantly, in population studies, the ST/HR index can increase the prognostic value of the exercise ECG by prediction of cardiac risk and mortality.

Acknowledgements

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