Point of View

A Lesson From the Controversy About Heart Rate Adjustment of ST Segment Depression

Marco Bobbio, MD, and Robert Detrano, MD, PhD

Every diagnostic instrument must be evaluated for a certain period of time before it can be assumed to be a constituent of the cultural background of physicians. It is subject to an “academic life” spanning from the time of its original description to its use as an outcome measure. Often, the first experiments appear more encouraging (the “promising reports”) than the observations that follow; daily practice defines the real value of any new instrument.

Ten years ago, the heart rate adjustment of exercise-induced ST depression, a noninvasive test, was purported to precisely predict not only the presence of coronary artery disease but also the number of obstructed vessels. This exceptional finding aroused doubts but was confirmed in all of the studies by one group of investigators in Leeds, UK. However, these results have never been duplicated in any other center. From then on, there has been a long series of reports (the “costly journey”) from authors determined to test the clinical usefulness of this method. Those studies achieved conflicting results so that a unanimous agreement still has not been reached, and the routine use of this method in exercise laboratories is uncommon.

Pathophysiological Background

This noninvasive test is a method of interpreting the electrocardiographic tracing during exercise; it is only one of several criteria currently applied to interpret the exercise test. With the conventional criteria, the ST segment depression of 0.1 mV or more for longer than 0.08 msec beyond the J point is evaluated. This is considered an index of ischemia, and it was expected to become more sensitive if adjusted with an index of oxygen demand. Obstructive coronary disease causes ischemia during exercise because the oxygen demand increases as the heart rate increases. If the ST segment depression occurs at a low heart rate, more severe coronary disease can be expected. In fact, it is well known that improving blood supply with bypass surgery will increase the threshold of ST displacement in a given patient.

Several methods have been proposed to normalize the ST segment depression by heart rate.

Historical View

To obtain a historical perspective of the debate, we listed (Table 1) and analyzed all published reports in order of date of journal acceptance. Since 1977, 29 original reports have been published. The 13 years of history of ST heart rate adjustment research can be divided into four phases: the first steps (1977–1978), the English period (1980–1984), the American period (1985–1986), and the period of expanding applications (1986–1990).

The First Steps (1977–1978)

At the end of the 1970s, research groups in The Netherlands and Hungary found a relevant increase in exercise test diagnostic accuracy with the ST heart rate adjustment using two different methods to adjust the ST segment depression for the heart rate increase. Simoons divided the ST displacement area by heart rate. This analysis was similar although not identical to the ST heart rate slope developed a few years later in Leeds. Berenyi et al calculated the slope of the relation between ST segment depression and heart rate.


The ability of heart rate adjustment to perfectly discriminate patients with different disease severities was postulated by the Leeds research group. These authors used a more sophisticated technique; they plotted the ST segment depression (as dependent variable) and the heart rate (as independent variable) in each of the 13 leads. Then, they computed a regression line from each group of three consecutive points and selected the highest slope with a statistically significant correlation coefficient as the test result. This method was called the ST/HR slope. In all six reports between 1980 and 1984, the Leeds group showed no overlap of values between patients without coronary artery disease and patients with one-, two-, or three-vessel disease. In their first report, Elamin et al stated that “in 64 patients, there are no false positive and no false negative results.”
The new method purported to predict the exact number of coronary arteries with critical stenoses. Their second report included the results from the same 64 patients with the addition of 56 additional subjects. This method was also applied to a different group of 142 consecutive patients. Furthermore, they showed that β-blocker therapy did not modify the value of the test because the drug reduces both the ST segment depression and the heart rate during exercise. This finding was very important because it was known that a high number of false-negative results induced by β-blocker therapy could affect exercise test results. However, the English period ends with the publication of two reports from two different centers in London. The authors made every effort to reproduce the method as previously described; in one case, the protocol was closely followed under the guidance of two Leeds researchers. Despite previous results, neither group was able to calculate the slope in all patients, and a perfect prediction was no longer demonstrated for either the presence or the severity of coronary artery disease.


At the beginning of 1985, the first of a series of studies done at the New York Cornell Medical Center was reported. Unlike the Leeds group, the Cornell investigators used only three electrocardiographic leads. The authors demonstrated that their method could greatly improve exercise test diagnostic accuracy in identifying very severe disease. They modified the method by including information regarding the exercise

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**TABLE 1. History of Heart Rate Adjustment of ST Segment Depression**

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>City</th>
<th>Patients (n)</th>
<th>Criterion</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td><strong>First steps (1977–1978)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Simoons</td>
<td>Rotterdam</td>
<td>138</td>
<td>ST⁶° plotted for HR</td>
<td>S</td>
</tr>
<tr>
<td>Berenyi</td>
<td>Balatonfured</td>
<td>33</td>
<td>ST/HR slope</td>
<td>S</td>
</tr>
<tr>
<td><strong>English period (1980–1984)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elamin</td>
<td>Leeds</td>
<td>64</td>
<td>ST/HR slope</td>
<td>PD</td>
</tr>
<tr>
<td>Kardash</td>
<td>Leeds</td>
<td>120</td>
<td>ST/HR slope</td>
<td>PD</td>
</tr>
<tr>
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<td>Leeds</td>
<td>60</td>
<td>ST/HR slope</td>
<td>PD</td>
</tr>
<tr>
<td>Elamin</td>
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<td>206</td>
<td>ST/HR slope</td>
<td>PD</td>
</tr>
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<td>PD</td>
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<td>46</td>
<td>ST/HR slope</td>
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<td>Quyummi</td>
<td>London</td>
<td>78</td>
<td>ST/HR slope</td>
<td>ND</td>
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<td>Balcon</td>
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<td>49</td>
<td>ST/HR slope</td>
<td>ND</td>
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<td>S</td>
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<td>New York</td>
<td>135</td>
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<td>Thwaites</td>
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<tr>
<td>Haraphongse</td>
<td>Edmonton</td>
<td>226</td>
<td>Sum ST/HR</td>
<td>S</td>
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<td>Finkelhor</td>
<td>Cleveland</td>
<td>64</td>
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<td>S</td>
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<td><strong>Period of expanding applications (1986–1990)</strong></td>
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<td>Detrano</td>
<td>Cleveland</td>
<td>303</td>
<td>ST/HR index</td>
<td>S</td>
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<td>Kligfield</td>
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<td>58</td>
<td>ST/HR slope vs. index</td>
<td>Both criteria similar</td>
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<td>ST/HR slope vs. index</td>
<td>Slope better than index</td>
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<td>Osaka</td>
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<td>S</td>
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<td>300</td>
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<td>Both criteria similar</td>
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<td>Bologna</td>
<td>42</td>
<td>ST/HR slope</td>
<td>ND</td>
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<tr>
<td>Decker</td>
<td>Rotterdam</td>
<td>345</td>
<td>ST/HR index vs. area</td>
<td>S</td>
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<tr>
<td>Okin</td>
<td>New York</td>
<td>100</td>
<td>ST/HR slope</td>
<td>Accurate computer model</td>
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<tr>
<td>Lachterman</td>
<td>Long Beach</td>
<td>328</td>
<td>ST/HR index</td>
<td>ND</td>
</tr>
<tr>
<td>Bobbio</td>
<td>Multicenter</td>
<td>2,270</td>
<td>ST/HR index</td>
<td>ND</td>
</tr>
</tbody>
</table>

Original reports are listed according to date of acceptance for publication. Results refer to standard evaluation of 0.1 mV or greater ST segment depression.

S, superior to standard ST criteria; PD, perfect discrimination of subjects; ND, not superior to standard ST criteria.
protocol and the exact method of measurement of ST depression.26 Furthermore, they observed that the method was affected by a previous Q wave myocardial infarction (reduced sensitivity) and by aortic regurgitation (reduced specificity).21

During the same period, the ST/HR slope improvement was refuted by a second study, which used a different group of patients, from the London National Heart Hospital,23 but it was supported by a study from the Cleveland Metropolitan General Hospital.24 Meanwhile, Haraphongse et al13 found that the ratio of the sum of ST segment depression in 12 leads and heart rate increased diagnostic accuracy of exercise testing; this method was never used by other authors.

The Period of Expanding Applications (1986–1990)

This period begins with the proposal10 of adjusting ST segment depression by dividing it by the difference between exercise and resting heart rate. This ratio was later called the ST/HR index.27 This method had been previously analyzed by the Cornell group,26 but it was judged less accurate than the ST/HR slope on a theoretical basis. The relation between ST segment depression and the heart rate is not usually linear. At the beginning of exercise, the ST segment does not change as the heart rate increases. When the ischemic threshold is passed, a progressive depression of the ST segment occurs despite small increments of heart rate. The measurement of ST/HR index represents a less-than-maximum value because it takes into account heart rate modifications that occur before ischemia. This method has the advantage of simplicity of calculation and can be used for screening purposes or applied to widely varying populations for retrospective analysis of available data.36

During the same period, several investigations from the Cornell group allowed the definition of a cutoff point for the ST/HR slope that was highly sensitive for the identification of three-vessel coronary disease28 and specific for excluding disease in subjects with a low likelihood.30 More recently, a computer program was found to be highly accurate in the estimate of ST/HR slope.33 When the ST/HR index was compared with the ST/HR slope in 58 patients,27 both ST adjustments were found to increase exercise test accuracy. In contrast, the slope criterion was more sensitive for the identification of patients with three-vessel disease.28 The index was more accurate than the standard ST segment depression criterion when applied to a population of 345 patients in Rotterdam31 but not when applied to 318 patients in Long Beach, Calif.34 Recently, the method has been applied to a multicenter data base of 2,270 patients from eight centers in three countries.35 Patients studied in three other reports16,32,34 are included in this data base. In only one of the eight centers was a statistically significant improvement of the new method observed when compared with the standard ST measurement.

Summary

To summarize the literature review, the heart rate adjustment appears to be able to perfectly discriminate patients with different numbers of diseased coronary vessels in one center, to increase the diagnostic accuracy of three-vessel or left main disease in eight centers, and unable to improve accuracy in seven centers. To explain those differences, several methodological and statistical biases have been considered. However, a recent report regarding the application of the method in eight centers and a meticulous literature review37 could not explain the superior performance in some laboratories.

An Exciting New Artist

We still do not know whether the new method is one of those medical innovations that McKinlay compared to some “exciting new artists”?2 for a certain period of time they enjoy public recognition, but afterward they quietly disappear into obscurity for inscrutable reasons. The disparity between the original optimistic results and the limited clinical usefulness may be in part ascribed to the fact that in most of the studies patients were selected according to several characteristics that could reduce the number of false-positive and false-negative findings (“avoidance of a limited challenge group”38). Other possible explanations are the use of “normal controls” in some of the studies39 and publication bias in early reports. Methodological differences have been discussed at length in other reports.1,34,38,39 Perhaps we will never know the precise methodological reasons for widely variable performances in different applicators of ST/HR methods. But we can at least learn to approach optimistic claims for new technologies with the proverbial grain of salt and to better understand the value and practical usefulness of the exercise test.

Acknowledgments

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