Random Exercise Stress Test in Diagnosing Effort Angina

Akiko Suyama, MD, Kenji Sunagawa, MD, Kiyoshi Hayashida, MD, Masaru Sugimachi, MD, Koji Todaka, MD, Yoshiaki Nose, MD, and Motoomi Nakamura, MD

To improve the performance of exercise stress testing in the diagnosis of effort angina while minimizing risks of serious complications, we evaluated an impulse response of ST changes, which is a transient ST response resulting from a hypothetical, strenuous-impulselike exercise, without actually imposing the strenuous load. To obtain the impulse response, subjects walked intermittently according to a computer-generated random binary sequence on a treadmill for 20 minutes (with a constant speed of 1.7 mph and a slope of 10%). We used Fourier transform for beat-to-beat changes in ST level and the binary sequence of exercise. We then determined the transfer function by taking the ratio of Fourier transformed ST level to exercise over the frequency range of 0.5 through 5.0 cycles/min. Converting the transfer function to the time domain yielded the impulse response of ST change. The subjects consisted of 49 patients (60±9 years) with effort angina, 13 patients with atypical chest pain (56±9 years), and 30 healthy, male volunteers (23±7 years). In 82 subjects (89%), the ST impulse response showed an initial depression followed by a smooth, gradual restoration toward the preexercise ST level (type I response). The average duration of the initial depression was 8±3 seconds in the healthy volunteers, whereas it was significantly prolonged to 23±14 seconds in effort angina (p<0.05). The depression in patients with atypical chest pain was not significantly different from that in the healthy volunteers. Although the level of exercise was milder in the proposed exercise test than in the conventional treadmill exercise test, the sensitivity and the specificity were significantly better in the proposed exercise test than in the conventional one in the same population. We conclude that this random exercise test is a sensitive, safe tool and is very accurate for the diagnosis of effort angina. (Circulation 1988;78:825–830)

A number of exercise tests have been developed to help diagnose ischemic heart disease.1-5 Despite the widespread acceptance of the exercise tests, they are not truly satisfactory as clinical tools for various reasons. First, their diagnostic value is not necessarily high. It is not unusual to have false-negative and false-positive responses with the conventional exercise tests. To improve the performance of conventional exercise tests, some investigators have developed elaborate quantitative scoring systems,6,7 which have significantly improved the detection of severities of coronary lesions. Despite such efforts, though, the values of these tests are still controversial.8,9 Second, to improve the diagnostic value, patients often have to be pushed to their physical limits. This inevitably increases risks of serious complications such as myocardial infarction and life-threatening arrhythmias.10,11

To overcome these limitations, we developed a random exercise test in which an impulse response of ST changes that result from a hypothetical, strenuous-impulselike exercise was computed. Even though the stress actually imposed in the random stress test was far milder than that in the conventional exercise tests, its diagnostic value was considerably better than the conventional tests.

Subjects and Methods

Subjects and Clinical Characteristics

We examined 30 healthy, male volunteers (aged 18–46 years; mean, 23±7 years) and 62 patients with complaints of chest pain (12 women, aged 35–80 years; mean, 57±9 years) of whom 49 patients

From the Information Science Laboratory for Biomedicine and Research Institute of Angiocardiology and Cardiovascular Clinic, Kyushu University Medical School, Fukuoka, Japan.

Supported by Research Grant 60C-3 for cardiovascular diseases from the Ministry of Health and Welfare, and Grant-in-Aids for Scientific Research (62570398) and Developmental Scientific Research (61870038) from the Ministry of Education, Science and Culture of Japan.

Address for correspondence: Motoomi Nakamura, MD, Research Institute of Angiocardiology and Cardiovascular Clinic, Kyushu University Medical School, 3-1-1 Maidashi, Higashiku, Fukuoka, 812, Japan.

Received November 20, 1987; revision accepted May 5, 1988.
had effort angina (aged 35–80 years; mean, 60 ±9 years), and 13 patients had atypical chest pain without any demonstrable organic heart diseases (aged 37–71 years; mean, 56 ±9 years). Twenty-three patients with effort angina had a history of myocardial infarction. In nine patients with effort angina, we applied the random exercise test before and after the treatments of percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery. In five volunteers and five patients with effort angina, we repeated the random exercise test to evaluate its reproducibility. Conventional treadmill exercise tests based upon Bruce protocol, thallium stress scintigraphy, and cardiac catheterization were performed in all patients to establish the diagnosis. Horizontal or downsloping ST depression of greater than 1 mm in any leads was considered as indicating a positive Bruce protocol stress test. Seventy-five percent or greater coronary stenosis was considered significant. These clinical data were summarized in Table 1. β-Adrenergic blockers, calcium antagonists, and nitrate were taken in 4 (6.5%), 19 (30.6%), and 18 (29%) patients, respectively. None of the patients was taking digitalis at the time of study. Exercise tests were performed at least 4 hours after the administration of drugs to standardize the experimental condition by minimizing the immediate drug effects.

**Random Exercise Test**

The examinee intermittently walked on a treadmill that moved at a constant speed of 1.7 mph with a fixed slope of 10% for 20 minutes after a pretaped, computer-generated, two-tone sound command. The exercise command signal was a random binary sequence with a minimal interval of 6 seconds. The exercise command signal had a constant power distribution in the frequency domain up to 5 cycles/min to avoid the distortion of the linear response resulting from the nonlinear system behavior. The average duty ratio of the command signal was 0.5. Therefore, the actual walking time was 10 minutes (i.e., 50% of the total test period) for the walking distance of 0.28 miles. On a four-channel FM magnetic tape recorder, we recorded the command signal and an electrocardiographic signal obtained from a chest lead (either from V_s or V_6).

**Data Analysis**

The FM tapes were played back and digitized at 200 Hz with a twelve-bit resolution on a laboratory computer system (PDP 11/44, Digital Equipment, Maynard, Massachusetts). After identification of the R wave, an ST level was measured in each beat at a prespecified time. The time to measure the ST segment was determined visually in each case. The

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Age</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Effort angina</td>
</tr>
<tr>
<td>OMI(−)</td>
</tr>
<tr>
<td>OMI(+)</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Atypical chest pain</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

LMT, left main trunk disease; OMI, old myocardial infarction; +, with OMI; −, without OMI.
average interval from the onset of QRS to the ST segment at which the ST level was measured was 143 ± 18 msec. The ST level thus determined and the intensity of exercise were linearly interpolated for every 0.5 seconds.

The impulse response can be obtained either by the time-domain approach through the direct deconvolution or by the frequency-domain approach. We used the latter to reduce the computational burden. As shown in Figure 1, the impulse response is obtained in the frequency-domain approach by converting the transfer function to the time domain. To determine the transfer function from the exercise stress to ST change, we first computed spectra of the exercise binary sequence and changes in ST by the fast Fourier transform. We divided the 20-minute periods of data into several segments and windowed them with the four-term Blackman-Harris window. We then transformed each segment by the fast Fourier transform and assembled the resultant spectra to reduce the variance of the spectral estimation. Second, we obtained 1) cross-power spectra between the changes in ST and the binary exercise sequence and 2) power spectra of the binary exercise sequence. The cross-power spectra were obtained by multiplying the conjugate of the exercise spectra to the ST change spectra. Third, computing the ratio of the cross-power spectra to the power spectra in each corresponding frequency yielded the transfer function. The ST impulse response was obtained by transforming the transfer function to the time domain through the inverse Fourier transform. This impulse response represents a transient, quantitative change in the ST level when a hypothetical, strenuous-impulselike exercise stress is imposed.

For statistical evaluation, we used the paired t test for matched data and analysis of variance with Bonferroni’s simultaneous comparison test or unpaired t test for unmatched data. A p value less than 0.05 was considered significant.

**Results**

**ST Impulse Response**

Patients neither complained of any symptoms nor showed obvious ST-T changes during and after the random exercise. The three major types of the impulse response are illustrated in Figure 2. In 82 of 92 subjects, the ST impulse response showed a transient initial depression followed by a slow or rapid restoration toward the preexercise level (type I response; Figure 2, left panel). In six subjects, the ST impulse response showed a transient initial elevation followed by a gradual decline toward the preexercise ST level (type II response; Figure 2, middle panel). In four subjects, the ST impulse response fluctuated (type III response; Figure 2, right panel). Forty-five of 49 patients with angina had the type I response, and the rest of the angina patients had the type II response. The angina patients with the type II response had a history of myocardial infarction. Ten of 13 patients with atypical chest pain had the type I response, and the rest had the type III response. Twenty-seven of 30 healthy volunteers had the type I response, two had the type II response, and one had the type III response. The types of the ST impulse response in each group of subjects are summarized in Table 2.

Because about 90% of subjects were type I responders, we primarily focused our analysis on the subjects who had the type I response. Figure 3 illustrates typical examples of ST impulse response of a healthy volunteer and a patient with effort angina. The amplitude of the ST impulse response was normalized by the maximum deviation of ST.

**Table 2. Clinical Profiles and Types of ST Impulse Responses**

<table>
<thead>
<tr>
<th>Effort angina</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMI(−)</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>OMI(+)</td>
<td>19</td>
<td>4</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>27</td>
<td>2</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>6</td>
<td>4</td>
<td>92</td>
</tr>
</tbody>
</table>

Values are numbers of subjects.
OMI, old myocardial infarction; +, with OMI; −, without OMI.
Type I, transient initial depression followed by a slow or rapid restoration toward the preexercise level; type II, transient initial elevation followed by a gradual decline toward the preexercise level; type III, ST impulse fluctuated.
The duration of ST depression of a healthy volunteer was 8 seconds and that of a patient with effort angina was 54 seconds. The average duration of the initial depression in the patients with effort angina (23 ± 14 seconds) was significantly longer than that of the healthy volunteers (8 ± 3 seconds, p<0.01) (Figure 4). The presence or absence of previous myocardial infarction associated with angina did not significantly alter the duration of the initial ST depression (23 ± 16 vs. 24 ± 14 seconds, NS). On the other hand, the average duration of initial depression found in patients with atypical chest pain was 9±2 seconds. This value was not significantly different from that of the healthy volunteers.

The effect of coronary artery bypass graft surgery is shown in Figure 5. The restoration of perfusion to the ischemic area clearly shortened the duration of initial ST depression. The average durations of the ST depression before and after such interventions were 27±12 seconds and 13±8 seconds (n = 9, p<0.05), respectively.

Reproducibility of this test was confirmed in five healthy subjects and five patients with effort angina. In both groups, there was no significant difference in the duration of the initial ST depression between the first and the second test (healthy subjects: 9±1 seconds vs. 10±2 seconds; patients: 37±19 seconds vs. 40±24 seconds).

Specificity and Sensitivity

To establish a diagnostic criterion of angina based upon the random exercise test, we evaluated the sensitivity and specificity as a function of the duration of the initial ST depression. If the ST depression longer than 12 seconds was used as a criterion, the sensitivity was 83%, and the specificity was 92%. If 14 seconds was used as a criterion, the sensitivity was 64%, and the specificity was 94%. These sensitivities and specificities were substantially better than those of the conventional exercise test with the Bruce protocol (50% and 72%, respectively), which was applied for the same population. Of interest, all eight patients with atypical chest pain who had shown a positive response for the conventional exercise test were correctly diagnosed by the random exercise test.

Relation Between the Duration of ST Depression and Severity of Coronary Lesion

We analyzed the relation between the duration of ST depression and the severity of coronary lesions. As shown in Figure 6, the duration of ST depression averaged 15±8 seconds (range, 7–30 seconds) in one-vessel disease (n = 23), 25±16 seconds (range, 9–50 seconds) in two-vessel disease (n = 14), and 40±13 seconds (range, 14–54 seconds) in three-vessel or left main trunk disease (n = 7). These differences were significant (p<0.05). One patient with effort angina with evidence of old myocardial infarction (6 months before the admission) had no significant coronary lesions at the period of the coronary angiography.
Diagnostic Value of the Random Exercise Test

The proposed random test has various advantages over conventional exercise tests. First, the sensitivity of this test in diagnosing effort angina was better than that of the conventional exercise test in the same population. The specificity was not compromised. Because sensitivity and specificity are influenced by a variety of factors, it was difficult to immediately extrapolate the results of this study to the general patient population. Indeed, the study population with whom we dealt had effort angina (about a 50% prevalence), atypical chest pain, and were healthy young men who were not susceptible to ischemic heart disease. Eight of 13 patients with atypical chest pain were referred to our hospital because of their abnormal exercise stress test. None of them, however, had mitral valve prolapse, hypertrophic cardiomyopathy, or hyperventilation syndrome, all of which often show the false-positive ST-T change by conventional exercise testing. Furthermore, the average age of the normal control subjects was not matched with the patient population. Therefore, one must be careful in generalizing the results of this investigation. Nevertheless, because this random exercise stress test had more reliable diagnostic values than conventional tests, it was a very attractive clinical tool in diagnosing effort angina.

Second, the stress load of the random exercise test was by far milder than that of the conventional tests. This has at least two advantages. One is that even patients with severely impaired cardiac function could bear this stress load. Practically any patient whose cardiac functions were New York Heart Association Class III or better could be safely evaluated by this random exercise test. With conventional exercise tests, it was necessary to push patients to achieve a certain level of exercise that would improve their diagnostic values. If the patients were unable to push themselves to that level because of noncardiac reasons, the diagnostic values of the exercise test would have been severely limited. The other advantage of the mild exercise is obvious. Although the morbidity and mortality are low in conventional exercise tests, serious complications such as myocardial infarction and life-threatening arrhythmias have been reported. With this random test, however, one could minimize the risk of serious complications. So far, there have been no significant complications in the random test.

Criteria for Diagnosing Effort Angina

In the conventional exercise tests, the magnitude of ST depression, as well as its time course, has been considered an important indication of myocardial ischemia. We considered exclusively, however, the time course (i.e., the duration of the initial depression of the ST impulse response) as the criterion of effort angina for the following reasons. In this preliminary study, we recorded electrocardiograms only from a chest lead (V5 or V6), regardless of the location of coronary lesions. Therefore, the recorded ST change did not necessarily reflect its maximal change. To detect maximal ST changes,
we need to evaluate the spatial ST vector. It is not yet known whether the determination of maximal spatial ST vector improves performance of the random exercise test.

As shown in the ‘‘Results,’’ a trade-off exists between the sensitivity and specificity, which has been shown also in the conventional exercise tests. Depending upon the purpose of the stress test, one may alter the criterion. For the purpose of identifying patients for further invasive coronary evaluations, a 12-second depression may be used as the criterion. With this criterion, the sensitivity was far better than that of the conventional exercise test for the same population, and it did not compromise specificity.

**Physiological Interpretation**

As has been indicated, about 90% of subjects showed the type I response. In the patients with effort angina, myocardial ischemia associated with a hypothetical strenuous exercise stress would be responsible for the prolonged depression of ST impulse response. In the healthy volunteers, however, the mechanism of the ST depression is not clear. Barnard et al19,20 and Foster et al21 reported that the sudden strenuous exercise could cause significant ST depression even in normal subjects. They attributed the ST depression to transient subendocardial ischemia. It is not yet known whether the transient ischemia is truly responsible for the initial depression of the ST impulse response in the normal volunteers.

**Conclusion**

In conclusion, the combination of improved diagnosis and of negligible risks of serious complications makes the random exercise stress test a very useful and a powerful tool for the diagnosis of effort angina.

**References**


**KEY WORDS**  • exercise stress testing  • effort angina  • system identification technique
Random exercise stress test in diagnosing effort angina.
A Suyama, K Sunagawa, K Hayashida, M Sugimachi, K Todaka, Y Nose and M Nakamura

Circulation. 1988;78:825-830
doi: 10.1161/01.CIR.78.4.825
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 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/78/4/825