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Exercise Testing
Part 1: Looking Beyond the ST Segment

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Although exercise electrocardiography is one of the most commonly performed, non-invasive diagnostic tests in the United States, it has fallen into relative disfavor in relation to other noninvasive modalities, including nuclear perfusion scintigraphy, PET scanning, and stress echocardiography.[1] Exercise electrocardiography, as well as noninvasive imaging studies, are commonly thought of as a means of *diagnosing* coronary artery disease.[2] That is, the clinician caring for a patient with known or suspected disease, is interested in knowing whether or not there is a coronary artery stenosis present that is severe enough to cause measurable myocardial ischemia.

According to recent American College of Cardiology and American Heart Association guidelines, the exercise electrocardiogram has two accepted roles in clinical care:[2,3]

- **for diagnostic evaluation**
- **for assessment of long-term risk in patients thought to be at intermediate or high likelihood of having significant coronary disease.[3]**

Although much literature has been written about the value of noninvasive testing for predicting risk, most clinicians still think of the exercise test as primarily a diagnostic tool. Furthermore, the main measure that attracts attention is the behavior of the ST segment during and after exercise. The first part of this review, demonstrates how the diagnostic model of employing exercise testing is fundamentally flawed and that the real value of the test lies in its strong ability to predict risk, particularly when measures other than the ST segment are considered. In Part 2 of this topic, in the next issue of *Cardiology Rounds*, the discussion will focus on the value of attenuated heart rate recovery as an independent predictor of increased mortality risk.

The diagnostic model

There are two fundamental problems with the diagnostic model of exercise testing, and in fact, of noninvasive testing in general. First, nearly all studies pertaining to the accuracy of non-invasive testing suffer from verification bias.[4-7] Second, the currently accepted gold standard – namely coronary angiography – is itself an inherently limited test.[8]

Nearly all literature regarding the accuracy of noninvasive testing involves cohorts of patients in whom noninvasive testing and coronary angiography were both performed as part of routine clinical care. While such cohorts are attractive and relatively easy to study, analysis of them suffers from a serious problem. The theory underlying evaluation of test accuracy assumes that

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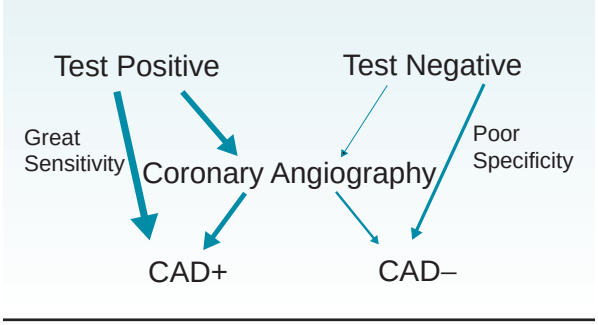
Figure 1: Verification bias – Among patients referred for noninvasive testing, some will have a "positive" result, while others will have a "negative result"(top line). Because physicians strongly believe that a positive result means that coronary angiography will show disease, patients with positive tests are much more likely to be referred for angiography (thick arrow) than patients with negative tests (thin arrow).
(Reproduced from Reference 9 with permission.)



the performance of the tests in question and the gold standard tests are two entirely independent events.[6] In fact, this is not the case when considering noninvasive testing for the presence of coronary disease.

As shown in Figure 1, a population of patients with known or suspected disease is referred for noninvasive testing to determine whether or not hemodynamically significant coronary stenoses are present.[9] Some of the patients will have a positive test while others will have a negative test. Because most doctors believe that a positive test means that coronary obstructions are more likely to be present, a fair number of patients with positive tests will be referred on to coronary angiography. Conversely, because doctors believe that a negative test implies a very low likelihood of obstructive coronary lesions, very few patients with a negative test will be referred on to coronary angiography. Thus, the cohort of patients who undergo coronary angiography is very different from the original cohort being studied, in that it is heavily enriched with patients who have had a positive noninvasive test.

Among the patients who undergo coronary angiography, some will have obstructive lesions and some will not. Among those patients who have obstructive lesions, a very high proportion of them will have had a positive noninvasive test to begin with. This has to be the case, because the vast majority of people who undergo coronary angiography were referred specifically because they had a positive noninvasive test. Thus, the sensitivity of the noninvasive test will look quite good. On the other hand, among those patients who do not show obstructive coronary lesions, very few will have had a negative noninvasive test. Again, this has to be the case because very few patients with negative noninvasive tests were referred to coronary angiography. The vast majority of patients with negative noninvasive tests never undergo coronary angiography and, therefore, their coronary anatomy must be considered unknown. Thus, the apparent specificity of the noninvasive test will appear to be poor. This bias, in which performance of a gold standard test is being influenced by the outcomes of the diagnostic test, is referred to as "verification bias" or "sequential workup bias."[4-7]

Is verification bias a serious problem in real clinical care?

To answer this question Froelicher and colleagues attempted to measure the true unbiased sensitivity of exercise electrocardiography.[5] They evaluated a cohort of over 800 men who were referred for exercise testing for evaluation of suspected coronary disease. All of these men agreed to undergo coronary angiography, irrespective of the results of the exercise test. The resulting sensitivity of the exercise electrocardiogram was only 45%, while the specificity was 85%. This contrasts with the results of a large meta-analysis that was based on literature in which verification bias was not eliminated, where the sensitivity and specificity of exercise testing were 70%.[10] Thus, verification bias turns out to be a real problem in that the true sensitivity of exercise testing is very poor, at less than 50%, while the specificity is reasonably good. Given that coronary artery disease is the number one cause of death in the developed world,[11] this extraordinarily poor sensitivity raises serious concerns.

Practicing clinicians may be unconsciously aware of this problem since, from clinical experience, they may sense that exercise electrocardiography has an unacceptably low sensitivity. As a result, they may refer more and more patients for exercise imaging studies.[1] However, exercise imaging suffers from the same kind of verification bias as exercise testing does. In fact, the true, unbiased sensitivity of stress echocardiography may be as low as 42%, while the specificity is reasonably good at 83%.[4] Similarly, the true unbiased sensitivity of nuclear imaging may be as low as 67%, with a specificity of 75%.[7] Verification bias may actually be a more serious problem with stress echocardiography or stress nuclear testing, because physicians give greater credence to imaging results and, therefore, their decisions regarding the performance of coronary angiography may be, in fact, more biased than in the case of stress exercise electrocardiography.

The second major problem with the diagnostic model of exercise testing is that the gold standard itself may be inappropriate. As discussed by Nissen and Topol, the

current accepted gold standard – the coronary angiogram – may have severe inherent limitations and may, in fact, substantially underestimate the burden of disease.[8] Furthermore, coronary angiography appears to be a less powerful predictor of coronary risk than noninvasive imaging.[12]

Exercise testing as a prognostic modality

If exercise electrocardiography, and in fact noninvasive imaging in general, is severely limited as a diagnostic test because of verification bias and an inherently limited goal standard, then what is the value of the test? The true value of exercise testing is in its ability to assess prognosis.

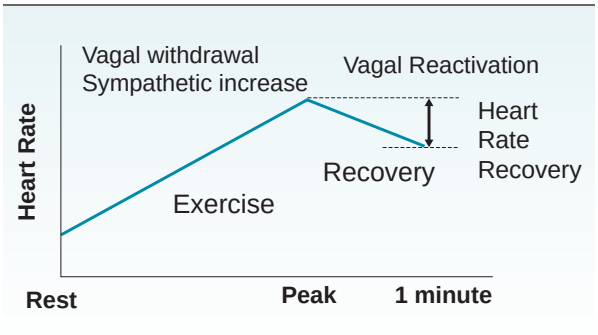
However, evaluation of the prognostic capabilities of a test is difficult because it requires large cohorts, systematically collected data, and long periods of follow-up.[13] During the past 10 to 15 years, a number of groups have been able to overcome these problems and report on the ability of exercise testing to predict death, and to a lesser extent, nonfatal coronary events.[2,14-18] The most important prognostic markers reported on include exercise capacity,[19-21] heart rate response during[22, 23] and after exercise,[18, 24-27] and the Duke Treadmill Score,[14,15,17,18,28,29] which is an amalgamation of exercise capacity and evidence of exercise-induced myocardial ischemia. Probably, by far the most important predictor of mortality is exercise capacity.[19-21,30-34] Classic literature dating back nearly 20 years reveals that patients with an exercise capacity of at least 10 metabolic equivalents are at extremely low risk for mortality, and gained no benefit from coronary bypass grafting, even when severe coronary disease is present.[35] Conversely, patients with impaired physical fitness are at high risk for death, even if significant myocardial ischemia cannot be demonstrated.[36]

Heart rate responses to exercise

During exercise the heart rate increases due to central nervous system withdrawal of vagal tone and an increase in sympathetic tone.[37] The increase of sympathetic tone is due to both central nervous system stimulation as well as to increasing levels of circulating catecholamines.[37,38] During recovery, there is rapid reactivation of vagal tone leading to a decrease in heart rate.[39] This decrease in heart rate immediately after exercise has been termed heart rate recovery (Figure 2).[40]

Why are the correlations of exercise heart rate responses with autonomic nervous system function clinically important? During the past 10-15 years, there has been increasing interest in noninvasive evaluation of autonomic nervous system function as a predictor of risk.[41-43]

Figure 2: Exercise heart rate changes during and after exercise. (Reproduced from Reference 40 with permission.)

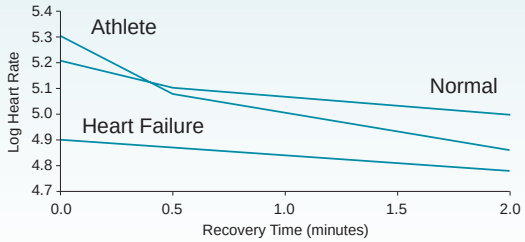


Using tools such as heart rate variability and baroreceptor reflex sensitivity, a number of groups have shown that disturbances of sympathetic and parasympathetic function are strongly predictive of risk of death in a wide spectrum of patients.[42-44] Furthermore, other investigators have demonstrated that chronotropic incompetence, or an inability of heart rate to rise appropriately during exercise, is correlated with decreased sensitivity to an overly active sympathetic nervous system,[45] while an attenuated heart rate recovery is reflective of decreased vagal tone.[39] Given the known associations of autonomic imbalances with mortality, and given the known associations of exercise heart rate responses with autonomic nervous system function, it was hypothesized that easily obtained measures of heart rate response in the exercise lab would be independently predictive of mortality.[22, 24]

Chronotropic incompetence

Chronotropic incompetence, or an inability to appropriately use up heart rate reserve during exercise, is a powerful predictor of risk.[22, 23] It was first described many years ago, when Ellestad noticed that a patient who had died suddenly and who had severe coronary disease on autopsy, had manifested chronotropic incompetence on an exercise test shortly before his death.[46] Assessment of chronotropic incompetence has been limited by the tight correlation of exercise heart rate response with age and functional capacity.[37] Wilkoff and colleagues,[47] as well as our group at the Exercise Stress Laboratory at the Cleveland Clinic Foundation,[23] have shown that measuring the proportion of heart rate reserve used in peak exercise is a way to describe chronotropic response that is independent of age and functional capacity.[47] Heart rate reserve can be considered as the difference between a person's maximum predicted heart rate, defined as 220 minus age, and that person's resting heart rate. The proportion of heart rate reserve used

Figure 3: Heart rate, after logarithmic transformation, during the first few minutes after exercise in athletes, normal subjects, and patients with heart failure. (Adapted from Reference 39.)



during exercise can be calculated as:

$$\%HRR_{Used} = \left(\frac{HR_{peak} - HR_{rest}}{220 - age - HR_{rest}} \right) \times 100$$

where HRR_{Used} is heart rate reserve used and HR is heart rate. For example, a 60-year-old with a resting heart rate of 70 has a heart rate reserve of (220 – 60 – 70) = 90 bpm. If he increases his heart rate to 140 bpm at peak exercise, he would have used ((140 – 70)/90) x 100 or 78% of his heart rate reserve. A person who is not on a beta blocker and fails to use 80% of their heart rate reserve is designated as having chronotropic incompetence.[47] This finding has been shown to be an independent predictor of mortality among patients not taking beta blockers.[22, 23, 48]

Heart rate recovery

In 1994, Imai and colleagues reported on a careful study of heart rate during the first few minutes after exercise in athletes, healthy normal volunteers, and patients with heart failure.[39] They noticed that after logarithmic transformation, heart rate during the first few minutes after exercise behaved in a bi-exponential manner. That is, among athletes and normal subjects, there was an initial steep fall in heart rate, which lasted approximately 30 seconds followed by a shallower fall. In contrast, patients with heart failure never had a steep fall during early exercise but rather had a shallow fall throughout recovery (Figure 3). After administering atropine, the initial steep fall decay in heart rate disappeared among the athletes and the normal subjects. Imai and colleagues, therefore, concluded that heart rate recovery after exercise, particularly during the first 30 seconds, is closely related to vagal reactivation.

At the Cleveland Clinic Foundation, we hypothesized that an attenuated heart rate recovery as a manifestation of decreased vagal tone would be an independent predictor of an increased risk of mortality. To confirm this hypothesis, we assessed approximately 2,400 patients referred for exercise nuclear testing during the early 1990s. Our findings regarding heart rate recovery, its prognostic significance, as well as its limitations will be discussed in Part 2 of this topic on exercise testing in the next issue of *Cardiology Rounds.*

Conclusions

In the exercise test, clinicians have available to them a very powerful prognostic tool, particularly when the right measures are taken into account. Exercise capacity, chronotropic response and heart rate recovery are strongly and independently predictive of risk of death. They are much stronger predictors of death than the classic ST segment response. However, when used as a diagnostic tool, exercise electrocardiography as well as noninvasive testing in general, is strikingly limited. Nearly all studies of test accuracy have been plagued by verification bias. In addition, the perceived gold standard, namely coronary angiography, is itself inherently problematic. Despite its seemingly low position on the totem pole, exercise testing has a bright future. By taking into account those measures of the exercise test that have real prognostic power, as well as factoring in clinical variables, the exercise laboratory has the ability to become a clinically useful "cardiovascular prognosis laboratory." Appropriate interpretation and use of the exercise test may lead to more appropriate utilization of other tests, as well as better allocation of treatment resources for patients at varying degrees of risk.[49]

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