Exercise Testing in Women with Suspected Coronary Artery Disease

Anthony P. Morise, MD

Exercise testing, defined as the treadmill exercise ECG without accompanying imaging, is a commonly used tool for the evaluation of atherosclerotic coronary artery disease. The question of how to best utilize this tool in women with suspected coronary disease is both important and challenging. It is important because women comprise over 50% of our population and coronary disease is the leading cause of death in women. It is challenging because, the role and value of the exercise test in women is clouded by misconceptions concerning the test's performance characteristics and the overwhelming concern to avoid a false positive study.

Many physicians consider the exercise test monolithically by factoring only ST segment changes into the interpretation of the test and the application of the results to patient decision-making. Clearly, when considered as an isolated variable, ST segment depression is, at best, a mediocre predictor of angiographic coronary disease. [slide 2] Meta-analyses as shown here demonstrate only fair sensitivity and specificity in women as well as men. Unfortunately, the populations used to derive these performance characteristics were affected by post-test referral bias, ie the preferential referral of ST segment positive exercise tests for angiography. However, adjusting for referral bias only serves to raise specificity at the expense of lowering sensitivity.

Many physicians do consider other information generated by the exercise test such as exercise capacity and peak heart rate. However, these are used many times to only determine the adequacy of the exercise test to assess the ST segment response. Thirty years ago, Myrv Ellestad's group demonstrated that the accuracy of the exercise test to predict the presence of coronary disease could be improved by combining ST segment responses with clinical and other exercise test variables into a multivariable format. Since then, many groups have confirmed this observation and produced multivariable equations using varied clinical and exercise test variables. While recommended for use by ACC/AHA guidelines, these equations have seen limited penetration into the clinical arena outside the institutions where they were derived. The principle reasons relate to their mathematical complexity and the lack of a practical means to use them.

My group along with the group at the Palo Alto VA have attempted to remedy this situation by developing simplified exercise tests scores specific for men and women to predict angiographic coronary disease when symptoms of suspected CAD are present. [slide 3] The women's score is shown here. On the far left are the variables incorporated. These include clinical as well as exercise test variables. The exercise test variables are the usual ones considered, ie ST depression, exercise heart rate, exercise induced angina. The clinical variables include age, presenting chest pain symptoms as defined by the Diamond criteria, diabetes, smoking, and estrogen status. For those unfamiliar with estrogen status, I will have more to say about this shortly. Each variable is assigned points with more points for lower heart rate, more ST depression, greater age, more typical anginal symptoms, the presence of smoking and diabetes, limiting angina, and negative estrogen status. Points are totaled for each variable yielding a total of from

0-100. [slide 4] As you will note, the total score can then be used to categorized a woman into a low, intermediate, or high post-exercise test risk group. The stratification into each of the 3 subgroups is good as shown here. [slide 5] This slide reveals that there is an incremental increase in the risk of MVD as well as any CAD as the exercise score rises.

Up to now, I have discussed how the scores as well as the exercise test have been used to predict angiographic coronary disease. More importantly, this exercise test score also predicts prognostic outcomes. [slide 6] In this slide, we note that the respective exercise score predicts survival in women as well as men. In this example, we see a clear separation of those with low risk from the rest.

[slide 7] Many of you may be unfamiliar with estrogen status. It is an important variable in women that helps to predict both cardiac prognosis as well as angiographic CAD likelihood. It simply defines a woman's hormonal status by considering whether she is pre- or postmenopausal. If post-menopausal, then Hormone replacement therapy (HRT) and ovary function status are considered. In general, women who are premenopausal or on HRT are considered estrogen status positive and would have points subtracted from the exercise score. On the other hand, women who are postmenopausal and not on HRT are considered estrogen status negative and would have points added to their exercise score. We have published data indicating that women who are estrogen status negative have 4-5 times the risk of angiographic coronary disease compared estrogen status positive women. This relationship is independent of age and all of the other variables in the exercise score. In addition, we have also recently published data concerning the relationship of estrogen status to cardiac prognosis. As shown here, estrogen status positive women have a better prognosis than estrogen status negative women concerning cardiac death and nonfatal infarction. This relationship is consistent within each of the estrogen status subgroups as noted here.

[slide 8] With this tool in hand, let us return to the ACC/AHA guidelines. Here we note that endorsements are dependent on pretest probability. Intermediate pretest probability is assigned the Class I indication. In other words, you should do it. Low and high pretest probability are assigned the Class IIb indication, ie. you may do it. [slide 9] Pretest probability is recommended to be determined using the Diamond-Forrester method, which considers age, sex, and presenting symptoms. As you can see, even in its simplest form, the table requires its presence to define pretest probability as low, intermediate, or high. One could guess at the extremes and usually be correct. However, patients who fall between the extremes would frequently be incorrectly assigned. Also, the DF method leaves no means to consider other important predictors such as diabetes, hyperlipidemia, or smoking. While the ACC/AHA guidelines recommend its use, they also indicate that other pretest probability methods exist. [slide 10] One such method that is referenced is shown here. This display uses a similar format as the exercise test score. As with the exercise test score, we see age, symptoms, diabetes, smoking, and estrogen status. Also incorporated are hyperlipidemia, hypertension, family history, and obesity. Based on age and sex, a base score is assigned with the addition (or subtraction) of points for symptoms and risk factors. Scores can range from 0-24 points with the assignment into low, intermediate, and high risk groups. [slide 11] This method was developed in an angiographic population and correlates linearly with both the presence and severity of CAD. Of note, within each risk subgroup, there is further stratification. In particular, note that those patients with scores of 0-2 have a 0% prevalence of CAD. Considering the way the score is configured, these 0-2 point patients will always be women who are young <50, estrogen status positive, with nonanginal chest pain and no more than 1 other nondiabetic risk factor. Keep this group in mind later when I discuss the appropriate selection of testing.

[slide 12] As with the exercise test score, despite being developed and validated in an angiographic population, it predicts prognosis as well. Here the outcome is all-cause mortality. [slide 13] When more cardiac specific outcomes such as cardiac death and nonfatal myocardial infarction are considered, there is a stepwise increase in risk as the score leaves the low risk range. Please note that those with score <=2 had no events. [slide 14] As shown here, we have validated the pretest score within the Womens Ischemia Syndrome Evaluation ie WISE population. As noted here, there is a clear separation of the 3 risk groups out to 1.5 years after the performance of the exercise test.

[slide 15] In considering the pretest risk groups, we have noted over the last 15 years that nearly 2/3 of women fall into the low pretest group. This is distinctly different than men where the majority of men fall into the intermediate pretest group.

I wish to next discuss how to select the appropriate stress test. These rules will not differ for men or women. To qualify for an exercise test without imaging one must have the ability to exercise and have an ECG that is interpretable. Therefore, no LVH with strain, LBBB, WPW, or more that 1mm resting ST depression allowed. These patients will require imaging with or without pharmacologic stress. RBBB and minor ST-T changes are perfectly acceptable for exercise testing.

[slide 16] This slide demonstrates the risk within each pretest group. Please note that I've chosen three different types of prognostic endpoints hopefully to satisfy all interested observers. These include all-cause death, cardiac death or nonfatal infarction, and cardiac death, nonfatal infarction, or revascularization. Irrespective of the endpoint chosen, there is a stepwise increase in risk as one progresses from low to high pretest risk. I wish for you to focus on the group with pretest scores <=2. As noted earlier, these women had 0% CAD prevalence and no events on 5 years of follow-up. On this basis, one could make a case that exercise testing as well as any stress test is not indicated in these very low risk women and that the source of their symptoms resides somewhere other than the coronary arteries.

[slide 17] Given its strong negative predictive value, the exercise test is ideally suited to the remainder of the low pretest risk patients. Systematic imaging in this group is not indicated. This recommendation is reiterated by the Appropriateness criteria for myocardial perfusion imaging.

At the other extreme are the high pretest risk patients with nearly a 2%/year risk of death. Because of this, one could make a case for these patients having a CAD-risk equivalent as assigned to diabetes and peripheral vascular disease. On this basis, patients should be treated as if they have coronary disease until proven otherwise. Depending on the case, one could justify just about any initial approach including the exercise test.

The intermediate pretest risk group as noted earlier could also undergo exercise testing without imaging as recommended by the guidelines. However, the Appropriateness criteria for myocardial perfusion imaging are in conflict with this recommendation. They suggest that it is appropriate to perform exercise imaging in intermediate pretest probability patients. Given that these recommendations are not based on randomized clinical trials, but rather clinical opinion, there exists a condition of equipoise between the two recommendations that cannot be resolved. My subsequent discussion of this matter will assume the use of the exercise test rather than imaging as the initial test.

[slide 18] Prior to moving on to the use of the test exercise score, let us first consider the impact of using both the pretest and exercise test scores. These data were generated from over 5000 patients from our laboratory, over 50% of whom were women. You will note that, when both the pretest and exercise test scores are considered, the majority, i.e. >90% of patients, fall into one of 3 groups. The majority within these 3 groups fall into the low post-exercise test risk group. A small percentage ie about 6% of all patients fall into the high pretest risk group. It is likely that rather than undergoing exercise testing, most high pretest risk patients undergo either catheterization or pharmacologic stress imaging as their initial evaluation. The remainder of my discussion will focus on the implications of the exercise test score results within each of the 3 pretest probability groups.

[slide 19] This slide displays data for only the low pretest probability group. No patients, men or women, are transformed from low pretest risk to high posttest risk.

Those that fall into the low posttest risk group are the majority. They should be directed to noncoronary evaluations or therapies as the likelihood of CAD and a bad cardiac outcome is quite low. Those that fall into the intermediate posttest risk group are a very small group but have a higher risk of bad outcomes. These patients should be directed to follow-up imaging to resolve why their exercise tests were abnormal.

[slide 20] This slide displays data for only the high pretest probability group. A very small number of women are transformed from high pretest risk to low posttest risk, but those that are have a good prognosis. Those that fall into the intermediate or high posttest risk group are the majority and they have >2% annual risk of a bad outcome. These patients should be directed to follow-up imaging either noninvasive or invasive to resolve why their exercise tests were abnormal. We were unable to find a lower risk subgroup within this group using other exercise test variables beyond the exercise test score. These overall findings reflect back to my earlier comments concerning how to evaluate high pretest risk patients, emphasizing individualized decision-making depending on patient-specific factors.

[slide 21] This slide displays data for only the intermediate pretest probability group. You might recall from an earlier slide that roughly 2/3 of this group ends up in the low posttest risk group. While these low posttest risk patients do have lower risk that the other patients at intermediate to high risk, their risk is not as low as the comparable low risk group from the low pretest probability group. For this reason, we recommend consideration of other exercise test variables not included in the exercise test score prior to discontinuing their coronary evaluation. Abnormalities in other nonscore related variables should prompt consideration of follow-up stress imaging. [slide 22] This slide lists those variables to consider. The Duke treadmill score, chronotropic and recovery heart rate responses, and exercise capacity should play an important role.

It is important to point that none of the above clinical process has been subjected to a randomized clinical trial to assess its efficacy and cost-effectiveness. However, this is true of much if not all of noninvasive stress testing methods we use on a daily basis. Despite this weakness, it is clear that the majority of women as well as men with symptoms of suspected coronary disease can be effectively risk stratified by the simple exercise test without the need to perform imaging.