ACSM's Certified News

The Professional's Choice

Volume 13, Number 4 **October-December 2003**

New Insights into the Clinical Exercise Test

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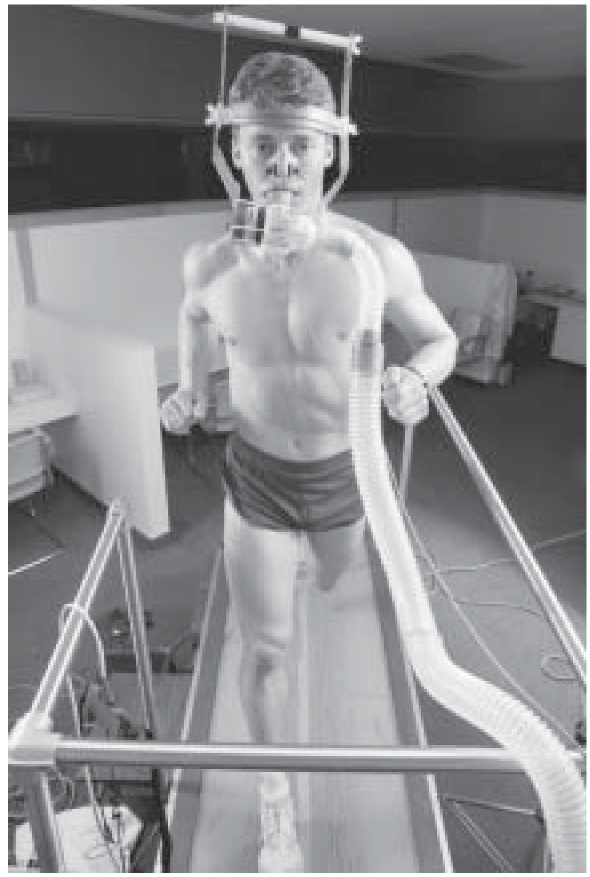

The use of exercise to stress the cardiovascular system has a long history in medicine, dating back to the early 1900s[1]. Historically, the diagnostic and prognostic applications of the exercise test have focused on ST segment changes, and with the ST segment response as the cornerstone, the exercise test remains the modality of choice for the initial evaluation of coronary artery disease (CAD)[2]. However, much has been written about the limitations of the ST segment. For example, test accuracy is lower in women, those with resting ECG abnormalities, and in populations with a low pre-test probability of CAD[2]. Because of these limitations and clinicians reluctance to stray from reliance on ST segment depression, many have turned away from exercise electrocardiography in favor of more expensive imaging modalities such as pharmocologic stress nuclear imaging or exercise echocardiography.

In addition, although a great deal of research has been performed regarding the prognostic applications of the test, many continue to view the exercise test as a diagnostic tool only. However, the standard exercise test has experienced a "renaissance" of sorts in recent years, fueled by studies on the diagnostic and prognostic performance of exercise test markers beyond the ST-segment[1-3] as well as a better understanding by clinicians of multivariate statistics. Test responses other than the ST segment that have received attention in recent years include exercise capacity, chronotropic incompetence, heart rate in recovery, and multivariate scores. In the following article, new research related to these novel exercise test markers is discussed in the context of their applications to the diagnosis and prognosis of cardiovascular disease.

Chronotropic incompetence

Elevated resting heart rate has been known for some time to be a strong marker for cardiovascular risk[4].

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Likewise, patients who demonstrate an inadequate rise in exercise heart rate (chronotropic incompetence) have a significantly higher rate of future cardiovascular events. Ellestad's landmark study of more than 25 years ago[5] demonstrated that patients who had an inadequate heart rate response to exercise, defined as those achieving less than 2 standard deviations below the expected heart rate based on age, had a significantly higher rate of cardiovascular events during a four-year follow-up.

These observations have recently been explored further by the development of a chronotropic index. In a series of studies from the Cleveland Clinic, a low chronotropic index, a measure of exercise heart rate that accounts for the effects of age, fitness, and resting heart rate, was associated with adverse outcomes independently of age, traditional risk factors, angiographic coronary disease and ischemia as determined by exercise echocardiography[6-8]. These studies have demonstrated an approximate doubling of the mortality risk among patients exhibiting an inadequate heart rate response to exercise.

An inadequate heart rate response to exercise appears to be a reflection of abnormal autonomic control of the heart[9], which helps explain the higher risk associated with this response.

Heart rate in recovery from exercise

A faster recovery of heart rate after exercise has long been thought to be related to better health and higher levels of fitness. While the rate at which heart rate recovers from exercise is considered to be a reflection of vagal reactivation[10], the prognostic utility of this response was not explored until recently. Cole et al[11] studied 2,428 patients referred for an exercise imaging investigation over a six year period and found that a decrease in heart rate <12 beats/min one minute into recovery from an exercise test was associated with a mortality risk that was four times that of patients whose heart rate recovery was faster than 12 beats/minute. Even when adjusted for potential confounders such as age, fitness, gender, and other cardiac risk factors, an abnormal heart rate recovery response was associated with a doubling of the mortality risk. These findings were validated in two other studies from the same group[12,13]. In a subsequent study among U.S. Veterans, 2,193 patients underwent both treadmill testing and coronary angiography over a 13 year period[14]. A decrease in heart rate of <22 beats/min at two minutes in recovery best identified high risk patients (associated with 2.6 times the mortality risk compared to a normal heart rate recovery response). Patients who exhibited a poor exercise capacity (<5.0 METs) and an abnormal heart rate recovery response had a particularly poor prognosis, with these patients exhibiting a 5-fold risk of mortality. Interestingly, heart rate recovery was not related to the diagnosis of CAD, a finding that suggests mechanisms responsible for autonomic dysfunction are independent of CAD.

Exercise capacity

Historically, the importance of exercise capacity has largely been discounted because clinicians have generally focused attention on the ST segment response to exercise. However, it is now appreciated that exercise capacity is one of the strongest independent predictors of all-cause and cardiovascular mortality. Recent studies from the

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ACSM's Certified News (ISSN# 1056-9677) is published by the American College of Sports Medicine Committee on Certification and Registry Boards.

Frequency: Published electronically four times a year (quarterly). The April and October issues are also available in print form.

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Cleveland Clinic, the Mayo Clinic, and the Veterans Administration (VA) have documented the importance of including exercise capacity in the risk paradigm among patients referred for exercise testing. In the VA study, exercise capacity was recently demonstrated to be a stronger predictor of mortality than all the other established predictors of cardiac risk, including smoking history, hypertension, diabetes, and other exercise test responses[15]. Blair and colleagues[16] demonstrated a 7.9 percent decrease in mortality for every one minute increase in treadmill time (the equivalent of approximately 1 MET) with serial testing among nearly 10,000 subjects followed for a mean of 4.9 years. This suggests that individuals who can improve their fitness level even modestly can significantly improve their mortality risk.

Studies from the Mayo Clinic[17] and the VA[15] demonstrated that every one MET increase in exercise capacity was associated with reductions in mortality ranging between 12 and 18 percent. In addition, exercise capacity has been independently associated with mortality in several multivariate analyses, and has been shown to be important in predicting risk in patients with chronic heart failure (CHF). In fact, directly measured peak oxygen uptake has been shown to outperform METs estimated from exercise workload as well as other clinical factors among patients with CHF as a predictor of mortality[18]. These clinical factors include measurements commonly associated with risk in CHF such as ejection fraction, type of CHF, and even invasive measures commonly used to reflect the severity of CHF. As a result of these and other studies, guidelines from the ACSM and other major bodies have recommended the inclusion of ventilatory gas exchange in exercise tests performed to evaluate patients with CHF who are being considered for transplant listing[2].

Together, these studies demonstrate exercise capacity to be a remarkably powerful prognostic marker. Because exercise capacity is improved by exercise training, exercise programs have the potential to favorably modify the risk profile in many patients.

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Exercise test scores

Clinicians spend much of their time collating and analyzing many pieces of information on patients in order to best direct therapy or recommend further procedures. However, it has been demonstrated that this decision making process can be imperfect, with clinicians unintentionally prioritizing personal experience over clinical trial data[19]. One approach to solving this problem has been the development of clinical 'scores' derived from multivariate analysis. Multivariate analysis involves the use of validated statistical techniques to select, "weight", and combine variables to provide the best possible test accuracy. While these techniques have been used for many years in various areas of medicine, there has been particular interest recently in their application to exercise testing. Variables chosen from the analysis can be calculated by the clinician or more complex scores can be calculated by a computer.

Prognostically, scores have incorporated multiple exercise variables into simplified paradigms to extract the maximum information, summarize the most important responses, and obtain risk estimates without having to use complex regression formulae. These scoring algorithms are increasingly being provided in exercise testing software systems. Using this approach, studies have effectively classified patients into risk categories, allowing costly and invasive procedures to be reserved for those who are most likely to benefit. Thus, these scores have the effect of incorporating complex statistical techniques into a tangible management strategy. Recent scores have even been shown to be portable (i.e. validated in populations other than those from which they were derived), and have been validated in women[20]. Examples of some of the major exercise test diagnostic and prognostic scoring systems are listed in Table 1.

The most widely used exercise testing score is the Duke Treadmill Score, which was developed to aid the estimation of prognosis[21]. However, scores can also be used to aid in diagnosis. In terms of CAD, pre-test variables associated with cardiovascular risk such as age, smoking, gender and diabetes are combined with exercise test variables such as exercise capacity, ST depression and symptoms and have been shown to improve diagnostic test performance in the

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Table 1. Recent Examples of Cardiac Risk Scores from Populations Referred for Exercise Testing

Diagnostic Scores for Men and Women

Risk Factor	Circle one response per risk factor: Male	Circle one response per risk factor: Female	Score
Maximal Heart Rate	Less than 100 bpm = 30	Less than 100 bpm = 20	
	100 to 129 bpm = 24	100 to 129 bpm = 16	
	130 to 159 bpm =18	130 to 159 bpm =12	
	160 to 189 bpm =12	160 to 189 bpm =8	
	190 to 220 bpm =6	190 to 220 bpm =4	
Exercise ST Depression	1-2mm =15	1-2mm =6	
	> 2mm =25	> 2mm =10	
Age	>55 yrs =20	>65 yrs =25	
	40 to 55 yrs = 12	50 to 65 yrs = 15	
Angina History	Definite/Typical = 5	Definite/Typical = 10	
	Probable/atypical =3	Probable/atypical =6	
	Non-cardiac pain =1	Non-cardiac pain =2	
Hypercholesterolemia?	Yes=5	NA	
Diabetes?	Yes=5	Yes=10	
Exercise test-induced Angina	Occurred =3	Occurred =9	
	Reason for stopping =5	Reason for stopping=15	
Smoking?	NA	Yes=10	
Estrogen Status	NA	Positive= -5, Negative=5	
	Total Score:		

Risk refers to angiographic coronary artery disease
For males: <40 = low probability; 40-60 = intermediate probability; >60= high probability.
For females: <37= low probability; 37-57= intermediate probability; >57 = high probability.
From Raxwal V. et al CHEST 119: 1933-1940, 2001, and Morise et al. Am J Med 102: 350-356, 1997

Prognostic Scores

Duke Score
Exercise time – (5 x ST depression) – (4 x treadmill angina index)
Exercise time on Bruce protocol;, ST depression in mm; angina index = 0 for no angina, 1 if angina occurred, 2 if angina was reason for stopping

VA Score
5 x (CHF or digoxin use) + exercise-induced ST depression in mm + change in systolic blood pressure score – METs
systolic blood pressure score = 0 for >40 mm increase; 1 for 31 to 40 mm increase; 2 for 21 to 30 increase; 3 for 11 to 20 mm increase; 4 for 0 to 11 mm increase
Low risk (<1% annual mortality) is a score <-2; moderate risk (4% annual mortality) is a score >-2 to <2;
high risk (>7% annual mortality) is a score >2

Simplified VA Score
METs <5, age >65, history of CHF, history of MI
1 point for each "yes" response; score of 3 or greater has hazard ratio of 5

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order of 20 to 30 percent when compared to ST segment changes alone. In fact, in a recent study, such scores were demonstrated to outperform all but the most experienced cardiologists[22], a finding which suggests further application in providing a second 'specialist' opinion for the generalist.

Summary

Despite the development of more sophisticated and expensive imaging modalities, the standard exercise test remains a central tool in the management of cardiovascular disease. However, a low sensitivity for diagnosis in some populations and the inability of ECG changes to localize CAD have led investigators to consider refinements to the basic test. Focusing on exercise testing responses in addition to the ST segment, including the heart rate response to exercise and recovery, exercise capacity, and exercise test scores, permits a greater information yield from what remains a simple and inexpensive test. These new markers should be routinely included in exercise test reports when exercise testing patients with known or suspected cardiovascular disease.

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Continuing Education Self Test Answer Key for *ACSM's Certified News*, Vol. 13, No. 4 • December 2003

Self Test #1 Answers: 1.b 2.d 3.b 4.d 5.a

Self Test #2 Answers: 1.b 2.d 3.true 4.d 5.false

Self Test #3 Answers: 1.b 2.d 3.c 4.b 5.d

Self Test #4 Answers: 1.b 2.b 3.b 4.c 5.d