Interpretation of Exercise Test Responses: Recent Advances

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FRANKLIN: ***Interpretation of Exercise Test Responses: Recent Advances.*** *Exercise stress testing is generally recommended for the following reasons: to aid in diagnosing occult or suspected coronary artery disease; to evaluate cardiorespiratory fitness, expressed as metabolic equivalents; to assess the efficacy of interventions such as pacemaker implantation, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, medications, or physical conditioning; to assess the safety of vigorous physical exertion; to formulate a safe and effective exercise prescription; and to assess work-related capabilities. Despite the limitations of the standard exercise electrocardiogram for diagnosing obstructive coronary disease, with an approximate sensitivity and specificity of 75% and 85%, respectively, the exercise test continues to have substantial diagnostic and prognostic value when measures beyond conventional ST-segment depression are considered. Diagnostic capability may be enhanced by heart rate (HR) adjustment of the ST depression, expressed as the ST/HR slope or the ST/HR index. The enormous prognostic value of exercise testing is based on numerous variables, if optimally combined and interpreted, including the Duke treadmill score, the presence of bundle branch block, chronotropic incompetence, heart rate recovery, exertional hypotension, ventricular ectopy during recovery, and exercise capacity. Cardiopulmonary exercise testing also yields prognostic data (e.g., the VE/VCO_2 slope) and may improve the sensitivity of the stress test. (J HK Coll Cardiol 2010;18(Suppl 1:31-36)*

Duke treadmill score, Exercise testing, Prognosis

Introduction

Exercise tests are helpful in assessing functional capacity and the safety of vigorous physical exertion and have diagnostic and prognostic significance in regard to cardiovascular morbidity and mortality. By progressively challenging the coronary circulation with a higher rate-pressure product and contractile state, the myocardial aerobic requirements may gradually exceed the circulation's ability to meet the oxygen supply. Major coronary obstructions are generally heralded by myocardial perfusion abnormalities, ischemic ST segment depression, the onset of angina pectoris, or combinations thereof. Nevertheless, acute cardiovascular events often occur at the site of previously nonobstructive atherosclerotic plaques,[1-3] highlighting the limited sensitivity of exercise testing in apparently healthy, asymptomatic individuals.

Over the past decade, clinicians have increasingly relied on more sophisticated and expensive tests (e.g., exercise echocardiography, exercise testing with concomitant myocardial perfusion imaging [thallium chloride-201 or technetium Tc99m sestamibi scintillation imaging]), presumably because of their improved diagnostic accuracy. Yet, by incorporating several measurements into a mathematical formula or treadmill score,[4] and by considering baseline electrocardiographic (ECG) anomalies, hemodynamic responses and cardiorespiratory fitness, expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O_2/kg/min), conventional exercise testing may compare favorably (or even outperform) the newer, more costly, noninvasive studies.

This review summarizes recent advances in the interpretation of exercise test results, with specific reference to the quantitation of ST-segment depression, Duke treadmill score, bundle branch block (BBB), chronotropic incompetence, heart rate recovery,

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exertional hypotension, exercise-induced premature ventricular contractions (PVCs) and cardiopulmonary exercise testing, including the direct measurement of peak or maximal oxygen consumption (VO_2max) and anaerobic threshold.

Electrocardiographic Findings: Heart Rate Adjustment of the ST-Segment Depression

Electrocardiographic responses to exercise tests should be interpreted according to the medications taken and/or the resting ECG, either of which may preclude accurate assessment of the exercise ECG, the presence of BBB, the magnitude and configuration of ST-segment displacement (Figure 1), and the provocation of supraventricular and ventricular arrhythmias. Exercise induced ST-segment depression, using ≥1 mm ST-segment depression at 80 msec beyond the J-point, is widely accepted as an indicator of myocardial ischemia and significant coronary artery disease (CAD), especially when concomitant angina occurs.[5] However, these conventional criteria have significant limitations in diagnosing occult CAD, with an approximate sensitivity and specificity of 75% and 85%, respectively.[6] More recently, investigators have suggested that the predictive accuracy of exercise stress testing could be increased by relating the magnitude of ST-segment depression to the change (Δ) in heart rate (HR), expressed as the ST/HR slope (μV/bpm) or the ST/HR index (μV/bpm).[7] An ST/HR index >1.6 μV/bpm is consistent with the presence of obstructive CAD and predicts increased cardiovascular risk. An ST/HR slope is considered abnormal and markedly abnormal if >2.4 μV/bpm and >6.0 μV/bpm, respectively.[8]

Duke Treadmill Score

The Duke Treadmill score uses exercise time (minutes), ST segment displacement (millimeters), and an angina index (0, none; 1, mild chest pain occurring during the treadmill test; 2, moderate-to-severe chest pain, reason for terminating the test):

Treadmill Score = Exercise time – (5 x ST displacement) – (4 x Angina index)

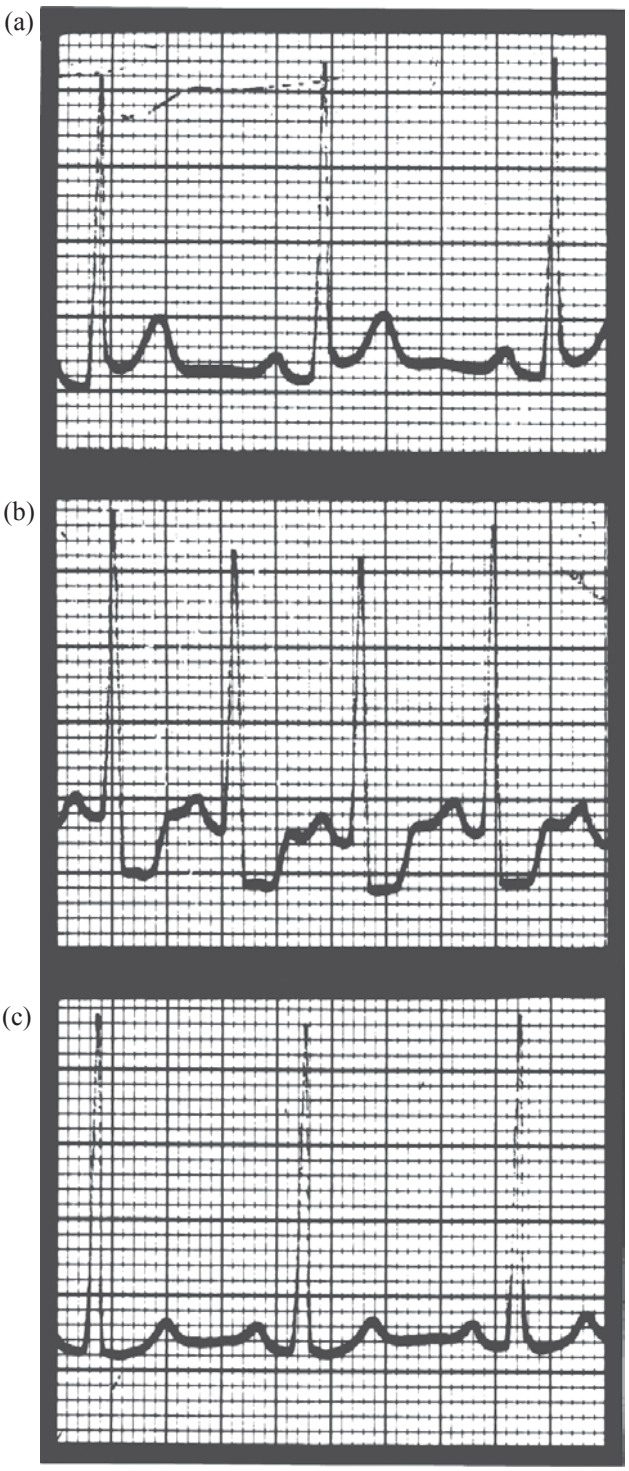

Figure 1. *(a) A patient's resting electrocardiogram (ECG; lead V_5) taken before exercise testing. (b) ECG obtained after several minutes of an exercise test showing significant ST-segment depression. The patient simultaneously reported mild-to-moderate substernal chest discomfort. (c) Resting ECG recorded 6 minutes after exercise, representing a normal configuration. The patient's symptoms had subsided.*

Mark et al[9] evaluated 2842 consecutive patients with chest pain who underwent both cardiac catheterization and treadmill testing, using the conventional Bruce protocol. Treadmill scores identified patients at low (≥5 points), moderate (-10 to +4), and high (≤11) risk of subsequent cardiac events, with corresponding 5-year survival rates of 93%, 86%, and 63%, respectively. Using this approach, it has been suggested that low-risk patients could be spared from additional diagnostic studies, whereas high-risk patients would be referred for cardiac catheterization.[6] Thus, for these patient subsets, treadmill scores render additional noninvasive testing unnecessary.

Bundle Branch Block

Hesse and associates[10] examined the prognostic significance of BBB, determined from the resting ECG, in 7073 adults with suspected CAD who were referred for symptom-limited nuclear exercise testing and followed for an average of 6.7 years. After adjustment for potential confounders, complete right BBB remained associated with a 50% greater risk of death, similar to that associated with complete left BBB. Although the mechanisms underlying this relationship remain unclear, the investigators suggested that complete BBB (right or left) may reflect a greater likelihood of left ventricular dysfunction, vulnerability to malignant ventricular arrhythmias, or both.

Chronotropic Incompetence

Sustained relative bradycardia (subsequently termed chronotropic incompetence) was first reported in the early 1970s. Ellestad tested a 50 year old man who had good exercise tolerance and no signs or symptoms of myocardial ischemia but was only able to attain a maximum heart rate of 110 beats/minute (bpm). The patient attributed his blunted heart rate response to his athletic background. Shortly thereafter he died suddenly, and the autopsy revealed severe CAD. Similarly, Hinkle et al[11] reported that the inability to achieve an expected heart rate on exercise testing identified a cohort of men who had an increased number of cardiac events during a 7-year follow-up.

Chronotropic incompetence can be determined for patients whose tests are terminated due to volitional fatigue (rather than abnormal signs and symptoms). Although it was initially designated as failure to achieve 85% of the age-predicted maximal heart rate,[12] this method may be confounded by age, aerobic capacity, and resting heart rate. Lauer et al[13] suggested that chronotropic incompetence was evident if less than 80% of the patient's heart rate reserve (calculated as 220-age-resting heart rate) was used at peak exercise. For example, a 50-year-old male, with a resting heart rate of 80 beats/minute in the upright position, attains a maximal exercise heart rate of 141 beats/minute at which point the test is terminated due to volitional fatigue. His heart rate reserve would be calculated as: 220-50-80 = 90 beats/minute. A normal response would be 80% or more of 90 beats/minute, added to the resting heart rate of 80 beats/minute, i.e., ≥152 beats/minute. Thus, this man would be classified as demonstrating chronotropic incompetence.

Recovery Heart Rate

The decrement in heart rate immediately after maximal exercise testing has also been suggested as an important predictor of mortality. Cole et al[14] studied 2428 consecutive adults (mean ± SD, age 57 ± 12 years, 63% men) who had been referred for exercise scintigraphy and followed for 6 years. The evaluation employed the symptom-limited Bruce treadmill protocol with a 2-minute cool-down walk, and heart rate recovery was measured at 1 minute after peak exercise. A delayed decrease in heart rate, defined as a reduction of 12 beats/minute or less from the heart rate at peak exercise, was associated with a relative risk of 4.0 for death (Table 1). After adjustments were made for potential confounding variables, including the workload achieved, the relative risk remained at 2.0 (1.5-2.7). It was concluded that this response, which may be a reflection of decreased vagal activity, is a powerful predictor of overall mortality, independent of exercise capacity, the use or nonuse of β blocker therapy, changes in the heart rate during exercise, and the presence or absence of myocardial perfusion defects. Other studies

have confirmed the potential value of heart rate recovery immediately after peak or symptom-limited exercise to predict increased mortality, independent of the angiographic severity of CAD.[15]

Exertional Hypotension

Exertional hypotension has been shown to correlate with signs or symptoms of myocardial ischemia, left ventricular dysfunction, and an increased cardiovascular mortality during follow-up. In a cohort of 1586 male cardiac patients, Irving and associates[16] found a negative correlation between the maximal systolic blood pressure during exercise and the annual rate of sudden cardiac death. Men with a maximal exercise systolic blood pressure <140 mmHg had a 15-fold increase in the annual rate of sudden death as compared with those whose pressures exceeded 200 mmHg (Table 2).

Exercise-Induced PVCs

Jouven et al[17] examined data from the Paris Prospective Study and evaluated the risk of death from cardiovascular causes in 6101 French men (42-53 years of age) without known or suspected cardiovascular disease who underwent conventional graded exercise testing. Subjects were prospectively classified as to the presence or absence of ischemic exercise ECGs and/or frequent PVCs. After a 23-year follow-up, both exercise-induced myocardial ischemia and the occurrence of frequent PVCs during exercise were independently associated with an increased risk of death from cardiovascular causes, with similar relative risks (2.63 and 2.53, respectively). More recently, researchers at the Cleveland Clinic Foundation reported that frequent ventricular ectopy during recovery, when reactivation of parasympathetic activity occurs, provides an even greater predictor of mortality than does frequent ventricular ectopy during exercise.[18]

Exercise Capacity

Previous studies in persons with and without documented CAD have identified a low level of cardiorespiratory fitness as an independent risk factor for all-cause and cardiovascular mortality,[19-21] including stroke.[22] Moreover, when it is combined with other clinical, exercise, or angiographic data, it becomes especially powerful in this regard. According to a recent analysis of studies to date in healthy men and women,

Table 1. Relation between an abnormal value for the recovery of heart rate and mortality[14]

Normal recovery (Reduction of >12 beats/minute)	Abnormal recovery (Reduction of ≤12 beats/minute)	Relative risk (95% CI)	p Value
Number of deaths/number of patients (%)			
93/1789 (5)	120/639 (19)	4.0 (3.0-5.2)	<0.001

CI=confidence interval

Table 2. Relation between maximal exercise systolic pressure and annual rate of sudden cardiac death[16]

Maximal systolic pressure (mmHg)	Annual rate of sudden death, per 1000
<140	97.0
140-199	25.3
>200	6.6

each 1-MET increase in exercise capacity confers a 13% and 15% reduction in all-cause mortality and cardiovascular events, respectively.[23] Moreover, participants with a functional capacity ≥7.9 METs had the most favorable health outcomes.[23]

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is essentially a standard exercise stress test that is complemented by simultaneous gas exchange measurements, including oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), respiratory exchange ratio (RER;VCO_2/VO_2), and the ventilatory-derived anaerobic threshold (V-AT), which signifies the break point in linearity when VCO_2 is plotted as a function of VO_2, expressed as a percentage of the VO_2max. This method has been reported to be a sensitive, reliable, noninvasive technique for the detection of the onset of metabolic acidosis.[24,25] The V-AT measurement is helpful because it usually represents the highest submaximal exercise intensity that may be sustained without inducing an appreciable increase in blood lactate.

CPET is considered medically necessary in the following patient subsets: assessment of exercise capacity and/or response to therapy in patients with heart failure who are being considered for heart transplantation; differentiation of cardiac versus pulmonary limitations as a cause of exertional dyspnea or impaired exercise capacity; and, evaluation of exercise capacity more accurately when estimates from exercise time or work rate may be unreliable.[26,27] Other recent studies suggest that directly measured VO_2max in morbidly obese patients may be helpful in risk stratifying those undergoing bariatric surgery.[28] Finally, two cardiopulmonary variables have now been reported to improve the sensitivity of the stress test, signifying exercise-induced myocardial ischemia: the course of the $\Delta VO_2/\Delta$ work slope and/or the presence of O_2 pulse flattening.[29]

Exercise tolerance or, more specifically, VO_2max, is one of the strongest and most consistent prognostic markers in persons with and without CAD.[30] Variables other than cardiorespiratory fitness, such as the VE/VCO_2 slope, oxygen uptake efficiency slope, V-AT, and multivariate scores have also been used to classify functional limitations, breathing economy, and, more recently, prognosis.[31] In particular, the VE/VCO_2 slope has been suggested as a marker of the severity of heart failure and appears to provide information for risk stratification that is independent from, and superior to, the highest VO_2 attained (VO_2 peak).[32]

Conclusions

Physicians who consider the above-referenced responses are likely to obtain additional diagnostic and prognostic information that may be helpful in risk stratifying patients and clinical decision making. In many instances, the findings from a conventional exercise test, if optimally combined and interpreted, can provide a predictive accuracy that is comparable to or greater than results obtained from more costly noninvasive studies.[30]

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