Application of exercise ECG stress test in the current high cost modern-era healthcare system

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ARTICLE INFO
Article history:
Received 25 January 2017
Accepted 14 June 2017
Available online 17 June 2017

Keywords:
Electrocardiogram
Stress tests
Exercise
Coronary artery disease
Cardiology
Primary care
Healthcare cost
Screening test

ABSTRACT
Exercise electrocardiogram (ECG) tests boasts of being more widely available, less resource intensive, lower cost and absence of radiation. In the presence of a normal baseline ECG, an exercise ECG test is able to generate a reliable and reproducible result almost comparable to Technitium–99m sestamibi perfusion imaging. Exercise ECG changes when combined with other clinical parameters obtained during the test has the potential to allow effective redistribution of scarce resources by excluding low risk patients with significant accuracy. As we look towards a future of rising healthcare costs, increased prevalence of cardiovascular disease and the need for proper allocation of limited resources; exercise ECG test offers low cost, vital and reliable disease interpretation.

This article highlights the physiology of the exercise ECG test, patient selection, effective interpretation, describe previously reported scores and their clinical application in today's clinical practice.

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1. Background

In 2012, greater than 4 million patients visited the emergency room for cardiovascular ailments including chest pain with an estimated cost of cardiovascular disease diagnosis >$300 billion. This cost is expected to rise to >$800 billion in 2030 in the United States of America alone. To complicate matters, a significant proportion of imaging cardiac stress tests are ordered with inappropriate indication for preoperative evaluation, asymptomatic patients, unindicated follow-up testing, etc. This results in a substantial financial burden (speculated at $6 to 10 billion for exercise single-photon emission computed tomography [SPECT] alone annually) raising the overall healthcare expenditure and restrict any reallocation of resources to the destitute population. Diagnostic imaging represents one of the fastest growing expenditure for Medicare. In the future, it is not wrong to expect rising healthcare costs, increased prevalence of cardiovascular disease and a rising need for proper allocation of limited resources. Under such circumstances, exercise ECG test offers low cost, vital and reliable disease interpretation.

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http://dx.doi.org/10.1016/j.ihj.2017.06.004
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2. Exercise ECG test

Appropriate patient selection is very important to prevent subjecting low probability patients to unnecessary interventions, or delaying them in high risk patients. The ideal candidate for a stress ECG test done to diagnose coronary artery disease (CAD) is an adult with a low or intermediate pretest probability of CAD based on age, gender and symptoms5,6 (Table 1). It is also indicated in patients with known CAD presenting with a change in clinical status, low to intermediate risk stable angina patients free of active ischemic or heart failure symptoms, 12–24 h after presentation7. High risk unstable angina patients should proceed directly to cardiac catheterization. Lastly, the test can also be used for risk stratification of patients prior to discharge and for pre-operative evaluation of selected patients. In a randomized trial of 457 patients, exercise ECG test was more cost-effective than myocardial perfusion imaging in low-probability patients while it was comparable in higher risk patients8.

For all patients, baseline ECG should be close to normal, but patients with a complete right bundle branch block or ST depression less than 1 mm can be assessed. Patients with ECG abnormalities such as an electronically paced ventricular rhythm, complete left bundle branch block, greater than 1 mm ST depression or pre-excitation pattern on the ECG are all inappropriate for this test9. Absolute contraindications to the test include patients with acute coronary syndrome in the last 5 days, poorly controlled heart failure, severe symptomatic aortic stenosis, acute endo-, myocardial infarction, severe peripheral vascular disease10,11. Even in patients who qualify, the test is not without an associated risk of mortality. Older studies noted a risk of approximately one cardiac arrest every 2000 stress tests in patients with heart disease, roughly 160 times greater than would occur spontaneously in such patients11,12. Risk is highest in patients being evaluated post-myocardial infarction or for inducible ventricular arrhythmias10.

The need for resting ECG with hyperventilation to rule out false positive responses related to hyperventilation has not been verified13. Variants of exercise such as bicycle stress tests may be better tolerated in some patients such as orthopedic or stroke patients13. Certain medications should ideally be stopped prior to the test- AV nodal blocking agents such as beta-blockers to reduce blunting the heart rate response, digoxin also to reduce artefactual effects on the ECG, nitrates which may increase false negative rates14.

3. Performance of the test

A standard 12 lead ECG should be obtained at baseline. The Mason-Likar modification in which the extremity electrodes are moved to the torso can be used to reduce motion artifact if the stress modality is exercise. It is important to remember that this modification may cause right ward axis shift, increased R wave amplitude and loss of Q waves in the inferior leads and development of new Q waves in aVL15.

It is important that the ECG be monitored carefully throughout the test and if the tracings have significant artifact, the test will need to be stopped. The development of ST elevations, ST depression > = 2 mm at < 5 METs affecting > = 5 leads and lasting > = 5 min into recovery, as well as sustained ventricular tachycardia are all parameters associated with adverse prognosis and multi vessel disease and should prompt the immediate termination of the test16,17. At least 85% of the maximum age predicted heart rate must be attained for obtaining a diagnostic quality test17. Lower heart rates decrease the sensitivity of the test dramatically.

4. Interpretation

The major findings are ST segment deviations and development of sustained arrhythmias. T wave changes have multiple causes and are non specific. Normally, the action potential duration is longer in the endocardium as compared to the epicardium18, and the ventricular repolarization proceeds from the epicardium to endocardium. The endocardium is excessively susceptible to ischemia19. With development of ischemia, the action potential duration is shortened and electrical gradients are created causing ST segment depression or elevation.

With ischemia, the ST segments become depressed and horizontal with the degree of displacement being proportional to the degree of ischemia10. Though ischemic ST segment changes are usually seen at peak exercise and often last several minutes into recovery, in 10% patients they may become manifest for the first time in the recovery phase. Occurrence of ECG changes early into the exercise and persistence into recovery are indicative of underlying multivessel disease and worse prognosis10.

Though the TP segment is the true isoelectric point, most often the PQ junction is the landmark chosen to assess the degree of displacement of the ST segment. The development of 1 mm (0.10 mV) or more of J point depression measured from the PQ junction, with a relatively flat ST-segment slope (< -7–10 mm/s), at 80 ms after the J point (ST80) in three consecutive beats with a stable baseline, is abnormal20. At heart rates higher than 130/min, the ST60 (60 ms after the J point) measurement should be used20. In patients with early repolarization, the ST depression should still be measured from the PQ junction and not from the elevated position of the J point. Horizontal or downsloping ST depressions are fairly specific for ischemia. If the ST segment depression is upsloping, the magnitude of the slope and the extent of depression determine if it is abnormal. If the ST depression is less than 1.5 mm with a rapid slope > 10 mm/ sec, this is a normal variant.

Table 1

| Age (y) | Gender | Typical Angina Pectoris | Atypical Angina Pectoris | Nonanginal Chest Pain | Asymptomatic |
|---------|--------|-------------------------|-------------------------|----------------------|-------------|
| 30–39   | Men    | Intermediate            | Intermediate            | Low                  | Very low    |
|         | Women  | Intermediate            | Very low                | Low                  | Very low    |
| 40–49   | Men    | High                    | Intermediate            | Intermediate         | Low         |
|         | Women  | Intermediate            | Very low                | Very low             | Very low    |
| 50–59   | Men    | High                    | Intermediate            | Low                  | Low         |
|         | Women  | Intermediate            | Low                     | Low                  | Low         |
| 60–69   | Men    | High                    | Intermediate            | Low                  | Low         |
|         | Women  | High                    | Intermediate            | Low                  | Low         |

Modified from Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing. A report of the american college of Cardiology/American heart association task force on practice guidelines (committee on exercise testing). J Am Coll Cardiol. 1997;30(1):260-3153.
than 1.5 mm depression with a slow upslope less than 10 mm/s is abnormal and maybe the only sign of obstructive CAD.

Important associated variables include degree and extent of ST-segment changes, time since initiation of exercise, associated symptoms such as angina, heart rate and workload at which the changes occur, persistence into recovery or associated drop in blood pressure.

ST-segment elevation may happen in the presence or absence of pre-existent Q-waves. ST elevations in the leads with prior Q-wave are indicative of previous MI with possible underlying dysskinetic or aneurysmal walls\(^{16}\), but not of ongoing ischemia. However, this may result in ST-segment depression in reciprocal leads giving a false positive result in those leads. On the other hand, ST-segment elevation \(>1\) mm at 60 ms after the J point, in leads without a Q wave and in three consecutive beats with a normal baseline is a very specific marker of transmural myocardial ischemia. ST elevation localizes the site of ischemia and identifies the coronary artery likely to be involved unlike ST depressions which are non-localizing.

In other cases, baseline ST-depression may return to ‘normal’ during exercise due to ischemia, though this phenomenon is rare\(^{10}\). Ventricular arrhythmias during exercise are commonly associated with ST elevations\(^{10}\). Other findings to look for include the development of bundle branch blocks. Left bundle branch block (LBBB) may develop in 0.4% of patients and carries an adverse prognosis with a 3 fold increased risk of death or major cardiac events. Rate related LBBB is due to fatigue of the left bundle and is transient, however these patients may ultimately go on to develop chronic LBBB. In the presence of LBBB, ST changes are non diagnostic. But, if the ST changes occur before the development of LBBB or after LBBB has resolved, then they can be interpreted in the usual manner. Right bundle branch block (RBBB) may develop in around 0.1% patients. In the presence of pre-existing RBBB, exercise induced ST depression in leads V1–V4 is common and non diagnostic, but ST changes in other leads can be interpreted in the usual manner. In the presence of ischemic changes on the ECG, transient intraventricular conduction delay (LBBB, RBBB or hemiblocks) may develop in 0.45% cases and are usually due to significant obstruction of the proximal left anterior descending (LAD) artery\(^{21}\).

5. Combining clinical and ECG parameters

As described above, a reliable and sensitive interpretation of exercise ECG test requires physicians to combine various variables obtained during the test. No single variable, including ST-segment change, has been shown to be accurate enough for wide clinical application. Horizontal or downward sloping ST-segment depression alone carries a low sensitivity <70%\(^{22}\). In the light of this, several indexes have been proposed that combine the clinical data with ECG changes and one such widely known score is the Duke treadmill score. The treadmill score(TS) is calculated using the duration of exercise in minutes(Et), maximal ST-segment change during or after exercise in millimeters(STmm) and ‘treadmill angina index’ (Ai) with 0 for no angina, 1 for non-limiting and 2 for exercise-limiting angina.

TS is calculated as Et – (5 x STmm) – (4 x Ai) with a score ranging from –25 (highest risk) to +15 (lowest risk)\(^{23}\). In a study of 613 patients, those with low risk score (score >=+5) exhibited a four-year survival as high as 99%\(^{24}\) in an outpatient setting. A study of 467 patients found a 5-year mortality of 3\(^{25}\) in low risk-score patients. Based on these results, it may be argued whether it is feasible to subject such low-risk score patients to angiography\(^{25}\), irrespective of their CAD status. Important exclusions from this study were patients with recent myocardial infarction or prior revascularization procedure and the applicability of the treadmill score may be reduced in elderly\(^{26}\).

Functional capacity is an important prognostic marker but lacks specificity as it is dependent on many factors including physical restriction, disability or deconditioning and lacks standardization\(^{26}\). In an old study on 1472 patients, McNeer et al.\(^{27}\) demonstrated that almost all the patients with positive results in Stages I and II of treadmill ECG test had significant CAD with >50% having three vessel disease. On the other hand, patients reaching Stage IV or higher with negative result had <10% prevalence of three vessel disease. Even the risk of missing significant CAD in such patients is offset by their high exercise tolerance and low predicted mortality\(^{27,28}\). Such patients with a high treadmill score, even in the presence of significant CAD, may not experience significant improvement in predicted mortality after angiography\(^{29}\). In a study by Borque et al.\(^{3}\), none of the 430 patients achieving a higher workload of >10 metabolic equivalent of task (METs, 1 MET = 3.5 mL/kg per minute of oxygen consumption, this corresponds to the resting state) in the absence of diagnostic ST-segment changes had significant ischemia on subsequent SPECT imaging. This represented 31% of their study population and an imaging study could have been excluded in such patients. Many such studies underline the current futile healthcare trend towards excessive reliance on imaging for confirmation.

Inability to increase heart rate in response to exercise i.e. inability to reach >85% of the age-adjusted maximum HR (220–age) is defined as chronotropic incompetence. It is independently associated with underlying CAD\(^{28}\), progressive heart failure\(^{29}\) and increased all-cause mortality\(^{30,31}\). But chronotropic incompetence may be confounded by the extent of patient’s maximal effort, premedication with nodal-blocking agents and early termination of the test\(^{32}\). To subvert some of these confounders, a lower threshold (<62% of maximum HR) was suggested to define chronotropic incompetence in patients using beta-blockers\(^{33}\) but this suggestion has raised some doubts\(^{34,35}\).

Another suggestion was using the extent of utilized ‘heart rate reserve’. This was called the chronotropic index calculated as [HR at peak exercise – HR at rest]/Heart rate reserve calculated as the difference between maximum age-predicted HR (220–age) and the HR at rest\(^{36}\). Assuming maximum exercise effort, a level <0.8 is associated with cardiovascular and all-cause mortality in general population\(^{10}\) and an index <0.6 in heart failure patients\(^{36}\). Similarly, slow recovery of heart rate is a mortality indicator independent of the patient’s exercise capacity\(^{37}\).

As the heart rate(HR) increases, myocardial oxygen demand increases independent of the underlying disease and the consequent ST-segment depression is directly proportional to the increasing demand. Consequently, heart rate adjustment of the ST depression was proposed as a more sensitive and specific marker of underlying CAD, corrected for increasing myocardial oxygen demand. This resulted in two new indexes – ST/HR slope and a similar ST/HR index. ST/HR slope was measured through complex computer algorithms requiring logistic regression analysis of ST depression relative to the heart rate change throughout the course of exercise\(^{38-40}\). The comparatively simpler ST/HR index was calculated as a ratio of the maximum overall ST depression in \(\mu\)V during exercise to the peak heart rate, was proposed as a more sensitive parameter of underlying CAD\(^{41}\). ST depression was measured at 60 ms from the J-point and leads V1, aVR and aVL were excluded due to false positives. The overall sensitivity was found to be 90% at a cutoff value of 1.6 \(\mu\)V/bpm\(^{22}\) and the benefit was most significant in women and in patients with equivocal test results.

Some studies that followed failed to duplicate such high sensitivity at higher heart rates\(^{40,42}\) while Kligfield et al.\(^{25,43}\) continued to be proponents of it.
6. Prognosis

There is a wealth of data outlining the prognostic information that can be obtained from a stress test\(^1\). The most important variables include the total exercise time and metabolic equivalents (METs) achieved, heart rate response (including chronotropic competence and heart rate variability) and the ST segment shifts with exercise. Borque et al.\(^4\) reported that patients reaching \(\geq 10\) METs had 0.1%/year cardiac mortality. Patients able to reach at least 75–85% of predicted maximum heart rate had lower risk of complication in the perioperative period\(^46\). Anginal chest pain during exercise is strongly predictive of underlying CAD\(^49\) and cardiac mortality\(^53\). Reduction in chronotropic indices in serial exercise stress testing was proposed as a marker of cardiovascular death in a 28-year follow-up study\(^56\). In a study of 1959, predominantly male patients, Leeper et al.\(^57\) demonstrated that a rapid initial rise in heart rate was associated with reduced mortality, though there have been conflicting reports of the same finding\(^45\). On the other hand, slow recovery of heart rate is a mortality indicator independent of the patient’s exercise capacity\(^7\).

In a study on 2275 patients referred for a technetium–99 m sestamibi stress test, Christian et al.\(^49\) demonstrated >95% positive predictive value for preserved resting LV function in patients with a normal baseline ECG, a finding similar to an older study\(^50\). Thus exercise ECG test alone may have been sufficient as the initial test in these subset of patients with normal baseline ECG for prognostication. Addition of imaging can then be reserved to patients with intermediate/equivocal results or prior revascularization\(^5\).

In summary, exercise ECG stress test offers a wealth of information that has been evaluated and confirmed in tremendous amount of literature in the past, most of which is beyond the scope of this article. It offers not only valuable diagnostic and prognostic information but also can help guide therapy individualized to the patient through exercise rehabilitation and identify patients with potentially poor future outcomes.

7. Limitations

The exercise ECG test alone has a lower sensitivity and specificity than imaging (reported at 68 and 77% respectively)\(^9\) but a higher negative predictive value (98% in vascular surgery patients\(^35\), 99.3% in a family medicine practice\(^52\)). This attribute of the test may be most valid in low risk patients, in whom CAD can be ruled out with considerable reliability in the absence of imaging and/or angiography. On the other hand, in intermediate to higher risk patients, exercise ECG test with or without imaging is useful only to confirm rather than rule out CAD\(^3\). Also, it has lower predictive value in elderly and women\(^13\) when used by itself. In fact in asymptomatic women, low exercise capacity, slow heart rate recovery and inability to reach target heart rate have been found to be more important predictors of outcome than exercise induced ECG changes. In patients with prior myocardial infarction or coronary interventions, additional imaging will offer increased sensitivity and specificity to detect and localize ischemia.

ST-segment depression alone has limited utility as a marker of ischemia with significant false positive results\(^17\). Moreover, exercise ECG test essentially requires a normal baseline ECG to give an interpretable data and this may exclude a significant number of patients. Intrinsical electrical conduction abnormalities resulting from left ventricular hypertrophy, left bundle branch block, medications such as digoxin can interfere with the accuracy of the data\(^17\).

Precaution must be exercised when interpreting the exercise stress test results to rule out CAD, whether with imaging or without, as their sensitivities may have been over-estimated due to referral bias. In the reported population studies, only patients with positive stress test results are referred further for angiography\(^46\) which may falsely increase the sensitivity. The patients with negative stress tests are not referred for angiography and may have underlying one or two-vessel CAD which may be clinically dormant or missed during the test itself due to limitations of the test\(^6\). Moreover, using angiography as a gold standard for detection of CAD over-estimates the actual prevalence of clinically significant obstructive coronary disease thus again blowing up the positive detection rates of these stress tests. If adjusted for the bias, the estimated sensitivities may fall significantly, effectively reducing the predictive value of any stress test with or without imaging\(^2\).

8. Conclusion

In today’s times of increasing healthcare costs, exercise ECG test offers a non-invasive, cost-effective, rapid and reliable prediction coronary artery disease and cardiac mortality under certain circumstances. The correct interpretation of ECG stress test should include a combination of history, clinical response to stress and ECG findings.

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