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TECHNIQUES
Narrative review

Exercise stress testing in clinical practice

Il test da sforzo nella pratica clinica

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Abstract

Exercise stress testing is an important diagnostic tool for evaluating patient's cardiovascular performance. The present review describes the accuracy and the value of exercise stress testing in different settings: after an acute coronary event, after percutaneous coronary intervention or coronary artery bypass graft; in patients risk assessment before non-cardiac surgery; in diabetic population; in patients with baseline electrocardiographic abnormalities. Moreover, this review provides insights relating to test accuracy in women and geriatric patients. Finally, this review explores new variables/parameters (dyspnea, chronotropic incompentence, heart rate recovery, functional capacity, integrated scores) that in the last few years added an incremental value to conventional analysis of exercise-induced angina or electrocardiographic changes.

Keywords

Exercise stress testing; Acute coronary event; Percutaneous coronary intervention; Coronary artery bypass graft; Dyspnea; Chronotropic incompentence; Heart rate recovery; Functional capacity; Women; Elderly

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Exercise stress testing after acute coronary event

The current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend submaximal or low-level ExT as early as 3-5 days after an uncomplicated coronary event prior to discharge unless the patient has undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery and been fully revascularised [1].
Maximal symptom-limited ExT can be performed 30 days after the coronary event. The submaximal exercise test is stopped when one of the following endpoints occurs:

- peak heart rate of 120 to 130 beats per minute or 70% of the maximal predicted heart rate for age;
- peak work level of 5 metabolic equivalents (METs);
- mild angina or dyspnea;
- exercise-induced ST-segment depression of 2 mm or more;
- exertional hypotension; or
- hree or more consecutive ventricular premature contractions.

Usually, if a patient is able to complete a stress test at an acceptable cardiovascular workload (5 or more METs) without any ECG changes, angina, hypotension, significant ST-segment depression or frequent ventricular premature contractions, he/she is deemed low-risk for a recurrent cardiac event during the next year [2].
Karlson et al showed that among patients hospitalised with a suspected or confirmed acute ischemic event but either no or only minor myocardial necrosis, the maximum working capacity at a symptom-limited ExT was independently associated with the long-term prognosis but not with other signs of myocardial ischemia [3]. Moreover, further predictors for long-term prognosis were age, a history of acute myocardial infarction, current smoking, and diabetes mellitus. Interestingly, mechanical revascularisation during the subsequent 5 years interacted with the influence of symptoms of angina during test and prognosis.
If the patient presents resting ECG abnormalities which preclude interpretation of exercise-induced ischemia, the addition of nuclear imaging as well as echocardiography is suggested. However, there is a general agreement that performing a symptom-limited ExT after an acute myocardial infarction (MI) using the Bruce protocol 3 days after admission determines a very low incidence of complications [4-6]. A meta-analysis showed that if the pre-discharge ExT is normal following an acute MI, there is a < 10% event rate at 1 year; if abnormal, the event rate increased to 10-20% [7]. Postinfarction functional capacity is also crucial: the ability to achieve an adequate cardiac workload (pressure rate product higher than 21,700) has been associated with an efficient myocardial blood supply and with a favorable 6-month prognosis [8].

Exercise stress testing after percutaneous coronary intervention

In patients who have undergone recent Percutaneous Coronary Intervention (PCI), recurrence of symptoms itself has low sensitivity and specificity for detecting restenosis and myocardial ischemia. ExT may provide useful information on symptoms and functional capacity of the patient; however, a meta-analysis showed that ExT alone has a poor sensitivity (46%) and a moderate specificity (77%) for the identification of post-PCI restenosis [9].
The use of nuclear imaging increases the sensitivity to 83% without affecting specificity [10]. In addition, ExT with imaging adds incremental information (ejection fraction and wall motion) and is useful to localise the region of ischemia as well as assists the interventionalist in identifying the culprit lesion [11-13]. Of note, symptom-limited ExT the day after stent implantation is safe [14].

In the first month post-PCI, an abnormal ExT may indicate inadequate intervention or revascularization result, or a successful result with impaired coronary flow reserve in the site [15].
Therefore, for routine follow-up in asymptomatic patients, it has been suggested to perform an ExT with imaging 2-3 months after PCI in order to avoid false positive results. At that epoch, ExT is useful to diagnose restenosis or new stenosis in asymptomatic patients as well as document functional capacity and aid in early identification of patients at risk for subsequent events [16].

Exercise stress testing after coronary artery bypass graft

In order to allow sternal healing and appropriate early rehabilitation, there is a general agreement on waiting 2-3 months after surgery before doing a symptom-limited ExT. In post-coronary artery bypass graft (post-CABG) patients with an abnormal baseline ECG which are non-diagnostic for ischemia, an imaging modality should be added. Exercise-induced ischemic ST-segment depression may persist when incomplete revascularisation is achieved, as well as in 5% of patients who have had complete revascularisation [17,18]. The sensitivity as well as the prognostic value of the test is greater in the late period (5-10 years after CABG) than in the early period (first year after CABG) [19,20].

Exercise stress testing in risk assessment before non-cardiac surgery

ExT is useful to identify coronary artery disease (CAD) in asymptomatic patients, especially in those who do not exercise regularly, or to stratify cardiovascular risk in patients with known CAD prior to non-cardiac surgery. Findings which increase risk of perioperative cardiac events include marked exercise-induced ST-segment depression or exercise-induced angina at low workloads, poor exercise capacity (< 5 METs), an abnormally low peak systolic blood pressure (< 130 mmHg), or a fall in systolic blood pressure during exercise > 10 mmHg below standing rest values [21,22].
According to 2007 ACC/AHA guidelines, continued emphasis should be given to preoperative clinical risk stratification, with noninvasive testing reserved for those patients in whom a substantial change in medical management would be anticipated based on results of testing [23]. Moreover, the implementation of the ACC/AHA guidelines for cardiac risk assessment prior to non-cardiac surgery in a consultant anaesthesiologist-led preoperative clinic reduced preoperative resources utilization, improved medical treatment and preserved a low rate of perioperative cardiac complications [24].
Notably, in clinical practice, ExT have a poor positive predictive value for identifying which patients will have a perioperative cardiac event, suggesting that perioperative MI's may not share the same pathophysiology as non-operative MI's [25,26]. In addition, patients with functional limitations such as arthritis or other medical problem will likely require an alternative form of stress test such as a pharmacological nuclear or echocardiographic stress test. To reduce the risk of these complications, some Authors have reported on the utility of intraoperative transesophageal echocardiography as a complementary monitoring tool in non-cardiac surgery. However, although this approach is now well established in patients undergoing cardiac surgery, there are no guidelines for intraoperative transesophageal echocardiography application in non-cardiac surgery, and little literature exists on patient outcome, logistics, financial impact, medico-legal implications and safety [27].
Finally, taking into consideration the higher risk of coronary angiography and revascularisation in high-risk patients, the current approach is moving away from extensive noninvasive preoperative risk stratification towards selective noninvasive testing and aggressive pharmacological peri-operative therapy [28].

Exercise stress testing in diabetic patients

Coronary artery disease is the leading cause of morbidity and mortality in patients with diabetes mellitus [29]. In fact, patients with diabetes have the same risk of myocardial infarction as do non-diabetic subjects with a history of infarction. For this reason, diabetes should be considered as a CAD equivalent [30].

Current diagnostic tools include ExT, stress echocardiography, stress myocardial perfusion imaging, and cardiac catheterisation [31]. Although cardiac catheterisation is useful, it is generally reserved for patients in whom invasive intervention is suitable. The American Diabetes Association (ADA) recommends ExT alone in symptomatic patients with 2 or more CAD risk factors or an abnormal resting ECG. Stress echocardiography is a useful, noninvasive procedure; however, there is limited experience with this technology in the diabetic population. Recently accumulated data support both diagnostic and prognostic roles for stress myocardial perfusion imaging, particularly with ECG-gated single-photon emission computed tomographic imaging. In symptomatic patients with diabetes, the presence and extent of abnormal stress myocardial perfusion imaging findings have been found to be highly accurate independent predictors of subsequent cardiac events: 18% to 26% of asymptomatic patients with diabetes have perfusion defects consistent with CAD. However, cardiovascular risk factors are not predictive of abnormal stress myocardial perfusion imaging findings even though duration of diabetes and abnormal ECGs are. A recent study showed that in diabetic asymptomatic patients, combining a myocardial scintigraphy with a maximal ECG stress test is effective in detecting more patients with coronary stenoses and predicting cardiovascular events [32]. However, ExT has a good negative predictive value for cardiac events (97%), is cheaper, and should therefore be proposed first [32].

Finally, related issues specific to diabetic patients undergoing ExT include:

- similar diagnostic sensitivity and specificity of ExT for identification of CAD in patients presenting with angina;
- lower diagnostic accuracy in asymptomatic diabetics, who may not manifest angina;
- reduced functional capacity, associated with increased cardiac morbidity and mortality;
- abnormal HRR.

Exercise stress testing in geriatric patients

The ever-increasing number of older patients requiring diagnostic and prognostic assessment for CAD has necessitated accurate, noninvasive techniques applicable to this age group [33]. Exercise electrocardiography is more challenging in the elderly. Elderly subjects are more likely to have baseline ECG abnormality rendering the ECG non-diagnostic [34]; and less likely to achieve adequate and diagnostic exercise workload due to arthritis, musculoskeletal disease, peripheral arterial disease, and reduced cardiopulmonary reserve [35]. Of note, in old population with higher prevalence of CAD, a borderline exercise test is much more likely to indicate real disease than in a low-risk younger population. In elderly patients able to exercise, workload achieved is independently predictive of cardiac morbidity and mortality [36,37]. Although the performance of exercise stress testing may pose several problems in older patients, it is not contraindicated [38]. Recently, McAuley et al [39], using ExT in healthy elderly men, observed independent and joint inverse relations of body mass index and cardiorespiratory fitness to mortality, suggesting fitness and fatness as mortality predictors in these subjects. For those patients with a non-diagnostic ECG or not able to exercise or achieve an adequate workload, adjunctive imaging may determine the extent and severity of ischemia with more accuracy [33,34].

Patients with left ventricular hypertrophy on their baseline ECG

ExT has been demonstrated to be sensitive (68% vs. 72%) but not so specific (69% vs. 77%) for detecting CAD [40]. Most testing labs will require ≥ 2 mm of ST-segment depression in the presence of left ventricular hypertrophy by Sokolow-Lyon (voltage) criteria to report a significant ST-segment change [40]. The major reason behind the false positive ST-segment changes is the mild subendocardial ischemia secondary to concentric hypertrophy and microvessels, in the setting of relatively normal epicardial coronary arteries.

Patients with a right bundle branch block on their baseline ECG

Patients with right bundle branch block (RBBB) typically manifest wide QRS complexes and T wave inversion in precordial leads V1-V3 on their baseline ECG, so exercise-induced ST segment depression is non-diagnostic if it occurs in leads V1-V3 [40]. However, in the remaining leads, ST-segment changes are diagnostic for ischemia, with the resulting sensitivity and specificity being similar to a patient with a normal baseline ECG. Therefore, it is still considered appropriate to perform ExT without imaging as an initial test in patients with RBBB.

Exercise stress testing in women

In women, sensitivity (61%) and specificity (69%) of ExT for detecting CAD using ST-segment changes or exertional angina are significantly less than for men [41]. However, low exercise capacity, abnormal HRR, inability to achieve target heart rate, and integrative scores were independently associated with increased cardiovascular and total mortality. Several reasons for the lower test accuracy in women should be considered. Women have a lower exercise capacity and achieve target heart rate less often than age-matched men [41]. Furthermore, women present with manifestations of CAD at an older age than men and thus unable to achieve as great a workload [42]. Women more often have resting ST-T changes and lower ECG voltage [41]. Finally, sex hormones (estrogen) can affect ST-segment changes and have a digoxin-like effect. Premenopausal women are more likely to have false positive ExT than postmenopausal women, and false positive tests occur more frequently when estrogen levels are high [43]. Postmenopausal women on hormone replacement therapy with estrogens showed an increase in false positive ischemic ST-segment depressions on ExT [44]. Women also present smaller coronary vessel size which may reduce the maximal flow heterogeneity and potentially decrease the amount of ST-segment changes. Finally, during the exercise portion of the ExT, women with moderate sized breasts may get excessive ECG motion artifact from the breasts pushing and pulling on adjacent skin and precordial ECG leads making it difficult to interpret ST-segment changes.

Exercise stress testing in women with polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in premenopausal women, with 6-7% prevalence worldwide, mainly characterised by chronic ovulatory dysfunction, insulin

resistance and hyperandrogenism [45]. Metabolic-hormonal features observed in PCOS represent an intriguing biological model illustrating the relationship between hormonal pattern and cardiovascular risk profile [46]. PCOS women, even at an early age, have a clustering of cardiovascular features, such as obesity, low-grade inflammation and metabolic syndrome [46,47].
ExT represents a useful tool at evaluating cardiopulmonary functional capacity and autonomic function in PCOS women [48-50]. Further studies are strongly encouraged in order to investigate the prognostic value of ExT in this group of patients.

Endpoints and post-exercise recovery

Criteria for the achievement of appropriate workload during ExT are reported in the box.
The test's capacity for detecting significant CAD is reduced whether a patient is unable to reach any of these endpoints for whatever reason [40]. Certain occurrences during the test strongly suggest an immediate stop of the ExT and have the patient sit down and recover. These include development of significant angina > 10 mmHg fall in systolic blood pressure, central nervous symptoms, signs of decreased perfusion, ischemic ST-segment elevation ≥ 1.0 mm in leads without Q waves (other than V1 and aVR), ischemic ST-segment depression ≥ 3.0 mm, equipment problems, request by patient to stop, or significant arrhythmia. Adverse findings during ExT which indicate future cardiac morbidity and mortality are shown in the box.
To note, the recovery stage is the only time where abnormalities manifest. Recovery continues until the patient's heart rate, systolic blood pressure, and ECG have returned to near baseline levels (usually within 9 min). In addition, because the patient is resting in recovery, the ECG has a good baseline with minimal motion artifact. During recovery, patients can have major ischemic ECG changes even when the exercise

Goals that the patient should achieve to obtain an adequate workload during ExT

- 85% of their maximal age-predicted heart rate, i.e. 0.85 × (220 – age of patient in years). This results in an increase in coronary blood flow of 2-4 fold in non-stenosed coronary arteries
- A pressure-rate product or double product of > 20,000, chosen because a pressure-rate product > 20,000 results in an increase in coronary blood flow of 2-3 fold in non-stenosed coronary arteries
- An ischemic endpoint (i.e. reproduced patient's usual angina so that they wish to stop or significant ischemic ST segment changes). Exercise-induced ischemic ECG changes occur more frequently, and usually precede onset of angina

Events that portend a poor prognosis during ExT

- Poor exercise capacity (< 5 METs)
- Abnormally low peak systolic blood pressure (< 130 mmHg) or a fall in systolic blood pressure during exercise of 10 mmHg or more below standing rest values
- Exercise-induced angina, especially at low workloads
- ≥ 2 mm of ischemic ST-segment depression at a low workload (≤ Bruce stage 2 or heart rate ≤ 120 beats per minute)
- Early onset (Bruce stage 1) or prolonged duration (> 5 min) ST-segment depression
- Multiple leads (5 or more) with ST-segment depression
- Exercise-induced ST-segment elevation (excluding aVR or leads with Q waves)
- Ventricular couplets, triplets, sustained (> 30 s) or symptomatic ventricular tachycardia
- Abnormal HRR

portion appeared normal. Also, tachy-arrhythmias including ventricular tachycardia and paroxysmal atrial fibrillation, or brady-arrhythmias such as second or third degree heart block, can occur.

ST-segment depression and ventricular ectopy in the recovery phase

The optimum ECG is more likely to be acquired early in recovery. Changes in recovery are just as significant for predicting risk for cardiac events (angina, MI, cardiac death) as those that occur during exercise [51]. Several studies showed that exercise-induced ventricular arrhythmias (defined as premature ventricular contractions > 10% of all ventricular depolarisation during any 30-s recording, or a run of three or more premature ventricular contractions during exercise or recovery) independently predict increased mortality [52]. One study of 29,244 men and women (mean age = 56 years; 70% men) who had been referred for ExT (with no history of heart failure, valve disease, or arrhythmia) found that frequent ventricular ectopy (> 7 premature ventricular contractions/min, bigeminy, trigeminy, couplets, triplets, ventricular tachycardia, flutter, torsade, or fibrillation) during recovery but not during exercise was an independent predictor of increased morbidity and mortality [53]. Despite these studies, it remains unclear whether exercise-induced frequent ventricular ectopy is an independent predictor or a marker of underlying heart disease.

Heart rate increase at the onset of exercise stress testing

The initial response of heart rate to dynamic exercise has been proposed as having prognostic value in limited studies that have used modalities other than the treadmill.
In a study population of 1,959 patients referred for clinical ExT, Leeper et al [54] reported that decreased heart rate changes at all initial relative exercise workloads were associated with significantly increased all-cause mortality. Interestingly, the heart rate rise at one-third total exercise capacity, however, was the only early heart rate variable that significantly predicted both all-cause and cardiovascular risk after adjustment for confounders. The Duke Treadmill score, however, was superior to all heart rate measurements in the prediction of cardiovascular mortality.

Heart rate recovery (HRR)

During recovery, vagal reactivation results in increased parasympathetic tone and a decline in heart rate. This decline is blunted with decreased myocardial function and reduced exercise capacity. Multiple investigators have confirmed that abnormal HRR, defined as failure of heart rate to decrease 12 beats or more during the first minute after peak exercise (while the patient remains standing) independently predicts an increased mortality in men and women [55,56]. Further, the greater the fall in heart rate in the first minute of recovery, the lower the subsequent mortality. An abnormal HRR likely reflects decreased vagal reactivation, and has been directly related to abnormal heart rate variability and insulin resistance [49,57,58]. Patients with a HRR of less than 25 beats per minute likely have autonomic imbalance; in one cohort of middle-aged men, this independently predicted sudden death [59].
It should be noted that both chronotropic incompetence and HRR predict cardiovascular mortality in patients referred for exercise testing for clinical reasons [60].
Myers et al [60] reported that chronotropic incompetence was a stronger predictor of cardiovascular mortality than heart rate recovery, but risk was most powerfully stratified by these two responses together. These Authors suggested that the simple application of heart rate provides powerful risk stratification for cardiovascular mortality from the ExT, and should be routinely included in the test report [60].

Systolic blood pressure recovery

The systolic blood pressure should fall rapidly after cessation of exercise by more than 15% at 3 min after stopping; myocardial ischemia may delay this decline [61]. Abnormal systolic blood pressure recovery is significantly associated with severe CAD [62]. Laukkanen et al [61] reported that a systolic blood pressure > 195 mmHg after exercise or a rise in systolic blood pressure of more than 10 mmHg/min for 2 min after exercise was associated with risk of future MI.

Exercise-induced bundle branch blocks and supraventricular arrhythmias

Exercise-induced transient left bundle branch block occurs in about 0.4% of patients, renders the left bundle branch block (LBBB) portion of the ECG uninterpretable for ischemia, and in one series independently predicted a higher rate of death and major cardiac events [63]. However, if ischemic ST-segment changes occur before or after the left bundle branch block has resolved, the ExT is still sensitive for CAD. If a transient LBBB develops at lower heart rates ≤ 120 beats per minute or with classic angina, this may correlate with significant CAD (often proximal stenosis of the left anterior descending artery) [64]. In contrast, if the LBBB develops at rates > 120 beats per minute it is more likely a rate-related phenomenon, and several studies have confirmed this to be associated with normal coronary arteries [64]. Exercise-induced transient RBBB is less common, occurring in about 0.1% of patients; a single study noted this was associated with CAD [64].

Supraventricular arrhythmias (atrial premature beats, atrial fibrillation, atrial flutter, supraventricular tachycardia) are commonly induced by exercise and seen in up to 10% of normals and in up to 25% of those with known or suspected CAD; they appear to be more common in patients with underlying heart disease. However, they are not diagnostic for CAD, nor do they predict adverse long-term cardiovascular outcomes [65].

Scores, functional capacity, and new developments

Integrated treadmill scores

Among the various scores that can be calculated based on traditional results as well as on other functional and hemodynamic aspects of the ExT that have prognostic value, the Duke Treadmill Score (DTS) is the most commonly used [66,67]. The DTS is easily calculated as follows:

$$\text{DTS} = \text{Exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{Angina index})$$

Where:

- Exercise time is calculated in minutes;
- ST deviation is the maximal exercise-induced ST-segment deviation in millimeters;
- Angina index is the exercise angina with 0 = none, 1 = non-limiting, 2 = exercise limiting angina.

The DTS is then classified into risk as follows: low risk ≥ 5, moderate risk -10 to +4, and high risk ≤ -11 [66,67]. Studies adopting the DTS score reported that CAD is more prevalent in men of all risk groups; however, amount and severity of disease increased from low risk to high risk in both genders as well as a higher mortality by all risk groups in men than women [66,67].

Functional capacity and metabolic equivalents

The metabolic equivalent is a unit of resting oxygen uptake which measures energy expenditure; 1 MET equals 3.5 ml oxygen uptake/kg/min. In studies of men and women referred for exercise testing, determination of exercise capacity in METs is a more powerful predictor of mortality than other established risk factors for cardiovascular disease [56,68]. Peripheral vascular endothelial function correlates with exercise capacity in both genders, even in the absence of CAD. Impaired functional capacity and abnormal HRR appear to be strongly and independently associated with lower socio-economic status [69,70]. Usually, major or sudden reductions in a patient's functional capacity (or MET level) should suggest further evaluation.

ExT in cardiac rehabilitation programs and exercise prescription

Cardiac rehabilitation in patients with CAD results in a substantial reduction in mortality and morbidity [71-73]. A typical outpatient cardiac rehabilitation program consists of weekly exercise for 12 weeks, allowing the development of an individualised exercise prescription that is safe and effective. The program should not improve the patients exercise capacity, but will also bolster confidence and psychological well-being, allow counseling on risk factor modification, and also establish a long-term exercise maintenance program [71-73]. According to AHA Guidelines, ExT should be used to risk stratify patients prior to starting any exercise program [74-81].

Conclusions

Implementing traditional variables with new parameters is diagnostically and prognostically important in patients undergoing ExT. ExT has an improved accuracy and is more clinically relevant when multiple risk parameters (ST-segment deviation, chest pain, exercise time, chronotropic competence, heart rate recovery, blood pressure recovery, ventricular arrhythmias) are incorporated into the final test result evaluation. These variables and related integrative scores, are important markers of current cardiovascular functional status, and also predict future morbidity and mortality. Novel variables and scores could help stratify risk, and so should be an integral part of the ExT report.

Questions for further research:

Implementing traditional variables with new parameters is diagnostically and prognostically important in patients undergoing ExT. Novel variables and scores could help stratify cardiovascular risk especially in women and geriatric patients; and so should be an integral part of the ExT report.

The review in brief	
Clinical question	This review aims at analysing the usefulness of exercise stress testing (ExT) as a diagnostic tool for evaluating patient's cardiovascular performance in different settings.
Type of review	Narrative
Search of the literature	PubMed, with keywords: exercise stress testing, acute coronary event, percutaneous coronary intervention, coronary artery bypass graft, dyspnea, chronotropic incompentence, heart rate recovery, functional capacity, women, elderly
Conclusions	We found that ExT has an improved accuracy and is more clinically relevant when multiple risk parameters (ST-segment deviation, chest pain, exercise time, chronotropic competence, heart rate recovery, blood pressure recovery, ventricular arrhythmias) are incorporated into the final test result evaluation. The present review dealt with new variables/parameters that in the last few years added an incremental value to conventional analysis of exercise-induced angina or electrocardiographic changes
Limitations	Search limited to the studies published in English

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