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Exercise Electrocardiography and Speckle Tracking Assessment of Ischemia

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Abstract:

Ischemic heart disease remains a leading cause of morbidity and mortality worldwide, with many patients presenting with angina despite non-obstructive coronary artery disease. Conventional diagnostic tools such as exercise electrocardiography (ECG) provide functional assessment of ischemia but are sometimes limited in sensitivity and specificity, especially in populations with microvascular dysfunction or subtle myocardial injury. Speckle tracking echocardiography (STE), through the evaluation of global and regional longitudinal strain, offers an advanced imaging modality that detects subclinical myocardial dysfunction even when left ventricular ejection fraction is preserved. Combining the functional data from exercise ECG with the structural and mechanical insights from STE may enhance diagnostic accuracy, improve risk stratification, and provide a more comprehensive assessment of ischemia.

Keywords: Ischemia; Exercise electrocardiography; Speckle tracking echocardiography; Global longitudinal strain; Microvascular angina; Non-obstructive coronary artery disease.

Introduction:

Ischemic heart disease remains the leading cause of cardiovascular morbidity worldwide, with many patients presenting with angina but no obstructive coronary lesions on angiography. This group, often referred to as ischemia with non-obstructive coronary arteries (INOCA), represents a diagnostic challenge, as conventional methods frequently underestimate ischemic burden **(1).**

Exercise electrocardiography (ECG) continues to be a first-line, widely available, and cost-effective functional test to provoke ischemia. However, its sensitivity and specificity are limited, particularly in detecting microvascular dysfunction or early myocardial abnormalities. Therefore, complementary diagnostic modalities are required to improve accuracy and guide clinical decision-making **(2).**

Speckle tracking echocardiography (STE) has emerged as a robust imaging tool capable of detecting subclinical myocardial dysfunction, even in the presence of preserved ejection fraction. Global longitudinal strain (GLS) derived from STE provides a sensitive marker of subtle ischemic injury, reflecting impaired myocardial mechanics not detected by standard echocardiography **(3).**

Recent evidence suggests that combining exercise ECG with STE parameters may enhance the detection of ischemia in patients with angina and non-obstructive CAD. This integrated approach can improve risk stratification and has the potential to identify patients at higher risk of adverse outcomes by linking functional ischemia with mechanical myocardial impairment **(4).**

In clinical practice, the approach to the evaluation of chest pain with suspected IHD focuses almost exclusively on the evaluation of atherosclerotic CAD. In the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR chest pain guideline, there are no sex-specific recommendations for the diagnostic evaluation of chest pain, and evaluation for ANOCA is recommended only after obstructive CAD is excluded. For patients with known CAD and stable chest pain, these guidelines recommend intensification of guideline-directed medical therapy **(5, 6)**.

For persistent symptoms in patients with known nonobstructive CAD, coronary computed tomography angiography (CCTA) with fractional flow reserve (FFR) or stress testing is recommended. Evaluation for ANOCA is recommended only after these tests yield negative results and the patient remains symptomatic. For patients with stable chest pain and no known CAD, evaluation for ANOCA is only recommended for intermediate/high-risk patients whose CCTA shows no obstructive CAD and who have evidence of ischemia on stress testing **(6).**

Assessing pretest probability

Our proposed approach begins with assessing the pretest probability of atherosclerotic cardiovascular disease (ASCVD). In women with persistent symptoms and no evidence of ischemia on traditional cardiac testing, there should be a high index of suspicion for ANOCA. In assessing the pretest probability of CAD, it is important to consider a patient's age, and risk factors and use existing standardized risk scores, such as the ASCVD score, to determine the likelihood of atherosclerotic CAD **(7)**.

It is important to recognize that the clinical presentation of ANOCA may not be distinct from that of ischemia due to CAD. Patients with ANOCA often experience anginal symptoms such as chest discomfort and shortness of breath. These symptoms may be exertional, as in CAD, but can also occur with emotional stress or without any provocation. Additionally, each subtype of ANOCA may present with differing symptoms **(8)**.

Patients with CMD experience exertional fatigue or dyspnea that limits usual exercise capacity, persistent chest pain after cessation of exercise, postexertional fatigue, as well as other symptoms such as shortness of breath, jaw pain, and profound weakness. Patients with vasospastic angina describe a sudden tightness in the chest that has a discreet onset, occurs at rest, and resolves quickly or persists at a lower level throughout the day, especially between night and early morning. Marked diurnal variation in exercise tolerance has been described. Symptoms are ameliorated with nitrate medications. Patients with MB are typically asymptomatic but may experience exertional or resting angina and less commonly, arrhythmias such as atrioventricular block, supraventricular tachycardia, or ventricular tachycardia **(9)**.

Women who have symptoms consistent with or suggestive of ANOCA are often perimenopausal or in the early postmenopausal period, and this presentation may be related to reduction in estrogen or other cardiovascular risk factors. Assessment of extracardiac factors not directly associated with ANOCA, but still risk-enhancing, is also important. These factors include the presence of chronic inflammatory disease; obesity; elevated C-reactive protein ≥2 mg/L; peripheral arterial disease; premature menopause (ovarian failure before the age of 40 years); a history of preeclampsia; and a family history of premature atherosclerotic disease (men aged <55 years or women aged <65 years). Additionally, although ANOCA can occur as an independent disease, it can also occur comorbidly with CAD. Thus, traditional cardiovascular risk factors, including hypertension, diabetes mellitus, and obesity should be assessed **(10)**.

To quantify a patient's risk of ASCVD, we recommend the use of a standardized risk assessment tool in the form of a validated risk score for the population being studied. The most commonly used score in the United States is the ASCVD risk score, a pooled cohort equation that estimates the 10-year risk of cardiovascular events. The Reynold's risk score (which additionally includes high-sensitivity C-reactive protein and family history of myocardial infarction in first-degree relatives prior to the age of 60 years), developed and validated in women, may also be appropriate **(11)**.

- **Noninvasive diagnostic testing**

Technological advances have led to the widespread availability of both functional (ie, stress testing) and anatomic diagnostic test modalities for the investigation of IHD. Overall, functional testing is most appropriate for documenting ischemia or assessing the symptom response to exercise. In patients with a low pretest probability of CAD, anatomic tests such as CCTA or invasive coronary angiography have a high negative predictive value for excluding CAD **(12)**.

The exercise tolerance test (ETT) or treadmill test is one of the most common initial tests used for the assessment of CAD. Historically, ETT was thought to have low sensitivity and specificity in women due to a higher rate of presumed false positive stress tests compared with men. However, more contemporary evidence based on invasive coronary Doppler assessment has shown that when CMD is added to the reference standard in addition to obstructive CAD, the specificity of ETT is excellent at 100%, and the false positive rate of ETT decreases from 31% to 0%. The misconception that ETT has

poor diagnostic value in women highlights a disparity that has existed and been perpetuated because obstructive CAD was used as the reference **(13)**.

Stress echocardiography with either exercise or pharmacologic agents can be used in the evaluation of angina. In contrast to radionuclide stress testing, stress echocardiography does not expose the patient to radiation and has been shown to have a high specificity for obstructive CAD. Pharmacologic stress echocardiography using vasodilators has been used to measure CFR, which may be helpful in the diagnosis of CMD, but this technique has not been widely adopted due to the expertise required for image acquisition **(14)**.

Radionuclide stress testing options include single photon emission computed tomography (SPECT) and PET-MPI imaging. Unlike PET stress testing, SPECT stress testing can be combined with an ETT to provide additional information regarding functional capacity. However, PET stress testing has increasingly been used in the assessment of ischemic symptoms given its advantages over SPECT imaging, particularly for women, including lower radiation exposure, superior imaging quality, accurate attenuation correction, and detection of regional perfusion defects **(15)**.

It can also measure rest and stress myocardial blood flow (MBF) and myocardial flow reserve (MFR), which can be used as a global measure of CFR. Notably, MFR has been shown to be predictive of all-cause mortality and major adverse cardiovascular events independent of angiographic stenosis severity. The use of PET-MPI has become more common in clinical practice, and it is an excellent noninvasive first step in assessing MFR and perfusion for the diagnosis of CMD **(15)**.

Stress cardiac magnetic resonance imaging (CMR) has higher resolution compared to SPECT or PET-MPI. Additionally, stress CMR has high diagnostic accuracy and can yield MBF and myocardial perfusion reserve index, providing valuable information regarding the presence of CMD. Both stress CMR with MBF and PET-MPI have a class 2A recommendation for the evaluation of ANOCA and are appropriate for initial assessment. However, stress CMR is not widely available in the United States **(16)**.

Anatomic testing with CCTA can be considered as an alternative to functional testing as an initial noninvasive investigation due to its higher accuracy in the detection of stenosis and nonobstructive lesions. In the 2021 chest pain guideline, CCTA has a class 1a recommendation for the evaluation of chest pain in patients with intermediate-risk and no known CAD. CCTA can provide additional prognostic information in women regarding the burden of atherosclerosis at a similar cost to that of stress testing. Importantly, CCTA is associated with significantly less exposure to radiation compared to nuclear stress testing. Furthermore, a unique advantage of CCTA in patients with suspected ANOCA is the ability to detect and characterize MB **(17)**.

- **Invasive CFT**

Although noninvasive diagnostic testing may be the initial test option for the assessment of patients who present with suspected IHD, CFT can definitively assess for CAD and characterize functional abnormalities within ANOCA. In 1997, the initial Women's Ischemia Syndrome Evaluation (WISE) trial was initiated to investigate IHD in women, including women with and without obstructive CAD, and a novel coronary reactivity testing protocol was developed using Doppler assessment. The WISE protocol raised awareness regarding the prevalence and prognostic implications of coronary vasomotor dysfunction, but the protocol could not be scaled to routine practice **(18)**.

Coronary thermodilution using a pressure- and temperature-sensor–tipped coronary guide wire has emerged as a readily available method for assessing CFR and IMR with high interoperator reproducibility. Historically, invasive coronary Doppler was the gold standard for the assessment of CFR and hMR, but this modality is currently off the market in the United States. Beyond FFR or nonhyperemic pressure ratios to assess translesional pressure gradients, invasive assessment of CFR and IMR can be used clinically to comprehensively assess the coronary circulation for causes of myocardial ischemia **(19)**.

In addition to wire-based testing, intracoronary ACh can be safely used to assess the endothelium-dependent vasodilatory pathway and identify coronary vasospasm and endothelial dysfunction. This test is performed by serially infusing ACh into the coronary arteries and evaluating for changes in coronary artery diameter, electrocardiographic changes, and patient symptoms. In healthy vessels with preserved endothelial function, ACh injection should lead to

vasodilatation. However, if there is endothelial dysfunction or underlying coronary vasospasm, ACh administration will lead to vasoconstriction **(20)**.

Exercise-induced cardiac troponin elevation

It is well accepted that short bouts of moderate intensity exercise taken regularly are beneficial for health. What is unclear is whether this still applies to those participating in strenuous and/or prolonged exercise. Some of this uncertainty has arisen from the growing literature demonstrating a rise in the cardiac biomarker, troponin (cTn), following endurance exercise. Understanding the significance of this is important. Firstly, to enable clinicians to give informed advice to those wishing to participate in such exercise and secondly to facilitate the interpretation of troponin levels in the context of an endurance event **(21)**.

cTn testing in the clinical setting

Due to their ability to detect cTn much earlier, high-sensitivity cTn (HS-cTn) assays have largely replaced those of standard sensitivity in the clinical setting. The enhanced sensitivity of these newer assays has led to the detection of cTn in healthy individuals which in conjunction with the existence of biological and analytical variability has made it harder to differentiate between a pathological and normal cTn value. To overcome this serial blood testing and the evaluation of troponin kinetics has become a fundamental component of the clinical assessment of chest pain patients **(22)**.

The change criteria for a pathological rise between the two blood sampling points is assay specific and depends on a variety of factors including the timing of baseline sampling and the onset of symptoms. The key is that any change detected is greater than the combined biological and analytical variation **(23)**.

A 20% or greater change from an elevated cTn value is set as the threshold for diagnosis of myocardial necrosis and represents a significant >3 standard deviations of variation associated with an elevated baseline concentration change in cTn on the basis of a 5–7% analytical total CV. For clinical situations where the baseline sampling value is below the URL a change in the range of 50–60% is needed. This is not error proof and thus it is recommended that if the clinical situation is ambiguous and the pre-test likelihood of disease high, additional sampling is performed **(24)**.

Current clinical guidelines for managing acute coronary syndromes (ACS) in patients without persistent ST-segment elevation recommend serial cardiac troponin (cTn) measurements, incorporating both rapid rule-out (0h/1h) and standard (0h/3h) diagnostic algorithms. Since patients presenting with post-exercise symptoms often fall into this category, applying these established cTn assessment protocols represents a clinically appropriate approach. The tiered testing strategy allows for efficient risk stratification while maintaining diagnostic accuracy in this patient population **(24)**.

cTn elevation following exercise

Earlier investigations using 2nd and 3rd generation assays reported significant elevations of cTnT and I following endurance exercise. Deriving common findings from these studies has been challenging for several reasons. Variables, including exercise modality, intensity and duration of exercise, are not standardized between studies. Furthermore, the use of different assays, each with its own sensitivity and specificity and threshold levels for detection and limit, makes cross comparison of results difficult. Finally, the timing for sampling troponin can differ between trials. As described later, the levels of troponin rise and fall over 24 h making it imperative to standardize sampling time points **(25)**.

Mechanism of cTn release

Several theories have been proposed to explain the mechanism underlying Tn release following exercise. Currently the most well received is that of increased membrane permeability of cardiomyocytes, whereby unbound cTn found in the cytosol diffuses across a concentration gradient from the intra- to extra-cellular compartment. The initial peak would represent this release of Tn through the sacrolemmal membrane with levels subsequently decreasing over 24 h reflecting the half-life and clearance of cTn subunits thereafter **(26)**.

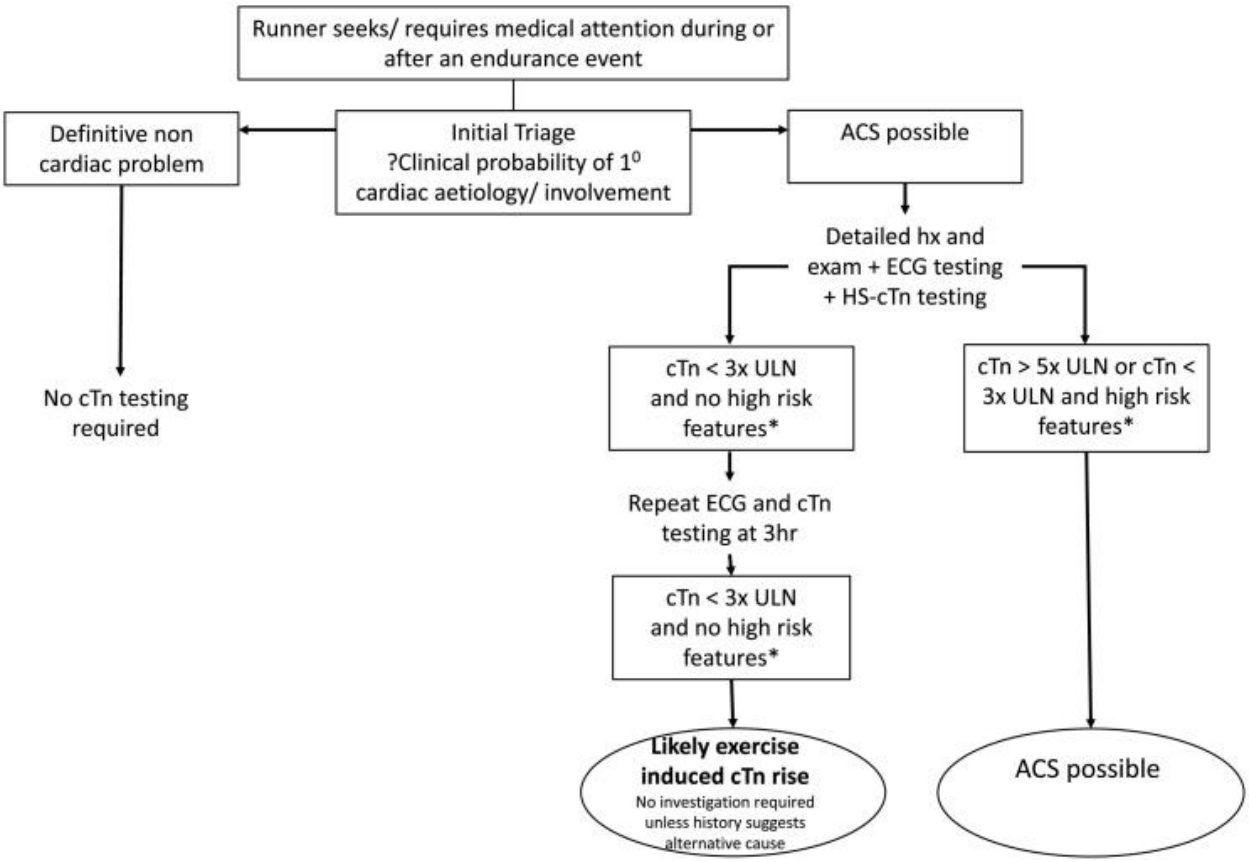

Figure 1: Algorithm outlining proposed management of patients with suspected ACS after exercise **(27)**.

Algorithm for the initiation of cTnT testing in patients with suspect non-ST-elevation ACS syndrome after exercise. This is proposed to supplement not replace standard clinical guidelines. High risk features include haemodynamic instability or shock, ongoing chest pain refractory to medical treatment, heart failure, life threatening arrhythmias or arrest and dynamic ST or T wave changes **(27)**.

It has been suggested that mechanical stress through the transient disruption (wounding) of the sarcolemma might be responsible for this increased membrane permeability. **(28)**.

An alternative explanation for exercise-induced troponin release involves integrin-mediated mechanisms. Integrins—transmembrane glycoproteins that facilitate cell-matrix adhesion—respond to mechanical stretch during hemodynamic stress, transmitting forces across cell membranes. This process activates intracellular signaling pathways associated with cardiac adaptation, potentially releasing troponin as a byproduct of physiological strain rather than irreversible injury **(29)**.

Experimental evidence suggests integrin stimulation can trigger reversible troponin release from cardiomyocytes without cell death. Studies using specific integrin-activating peptides demonstrate this phenomenon, showing troponin elevation without lactate dehydrogenase (LDH) leakage—a marker of irreversible membrane damage. These findings support the concept that troponin release during extreme exercise may represent a physiological response to mechanical stress rather than pathological injury **(30)**.

This mechanism could explain why endurance athletes frequently show elevated troponin levels despite no clinical evidence of myocardial damage. The integrin hypothesis aligns with observations of rapid biomarker normalization post-exercise and the absence of long-term cardiac dysfunction in affected athletes **(31)**.

Tn release following prolonged and/or strenuous exercise could be secondary to subclinical apoptosis or necrosis. The kinetics of exercise-induced cTn rise with a peak within the first 1–4 h and falling levels thereafter with resolution at

72 h make this suggestion unlikely. This is in contrast to the peak seen at 24 h after a type 1 MI peak with continued sustained levels for several days. Finally injured skeletal muscle may release proteins that are detected by TnT assays resulting in situations where elevated cTn values may originate from skeletal muscle. This as yet has only been seen in those neuromuscular conditions and its applicability to healthy participants completing a bout of exercise is uncertain **(31)**.

Speckle tracking echocardiography

It is widely known that echocardiography is an essential supporting tool for clinicians in the evaluation of coronary artery disease (CAD). Its application could vary between acute and chronic coronary syndromes (ACS and CCS); however, it has shown not only to aid diagnosis but also to provide useful prognostic information in this clinical setting **(32)**.

The gradual introduction of speckle tracking echocardiography (STE) into clinical practice and its validation for diagnosis and risk stratification in different cardiac disease with a great feasibility have allowed to appreciate its potential additive value also for patients with CAD **(33)**.

In fact, speckle tracking analysis is capable to assess typical ischemic subendocardial damage through several parameters: longitudinal strain (LS), which is the most used STE parameter to assess the early affection of subendocardial fibers of all cardiac chambers; bull's eye representation of left ventricular global LS (LVGLS) that provides a regional evaluation of LV injury according to coronary vascularization territories and the specific analysis of endocardial wall deformation properties with the three-layer analysis **(32)**.

These tools could be useful to promptly guide diagnosis in uncertain cases of ACS and to provide early detection of CCS. Moreover, speckle tracking analysis could be performed on stress echocardiography (SE) images to assess subtle myocardial damage in case of doubtful stress test results or to assess myocardial viability. STE was also shown to be a marker of myocardial fibrosis; therefore, it could represent a noninvasive marker of myocardial postischemic scar **(33, 35)**.

CAD Diagnosis Using Speckle-Tracking Echocardiography

Current guidelines highlight the utility of speckle-tracking echocardiography, particularly left ventricular global longitudinal strain (LVGLS), in diagnosing coronary artery disease (CAD) when standard wall motion analysis is inconclusive. In patients with chest pain but nondiagnostic ECG and biomarker findings, reduced LVGLS (typically > −18.8%) and global circumferential strain (GCS > −21.7%) demonstrate strong discriminatory ability in identifying significant coronary stenosis. This approach enhances diagnostic accuracy beyond traditional wall motion scoring, particularly in cases where ischemia is suspected but not visually apparent **(35)**.

LVGLS analysis also enables rapid assessment of regional myocardial dysfunction through polar map visualization. By segmenting the left ventricle into 17 regions, strain patterns can localize perfusion abnormalities corresponding to specific coronary territories. Additionally, this technique aids in differentiating acute coronary syndromes from Takotsubo cardiomyopathy—which typically shows apical strain impairment—and acute myocarditis, where strain abnormalities lack a coronary distribution pattern. These capabilities make speckle-tracking echocardiography a valuable noninvasive tool for refining CAD diagnosis and distinguishing it from other cardiac conditions with overlapping presentations **(36)**.

While speckle-tracking echocardiography provides valuable insights into myocardial function, some limitations should be acknowledged. Regional strain analysis has been questioned due to variability in measurements across different vendors and observers, reducing its reliability for segment-specific assessments **(37)**.

Instead of focusing on absolute segmental strain values, a more practical approach involves evaluating overall strain patterns to identify characteristic ischemic distributions. Left ventricular global longitudinal strain (LVGLS) remains the preferred diagnostic parameter due to its greater consistency. Additionally, technical challenges—such as tachycardia, poor ECG synchronization, and suboptimal imaging windows—often limit strain analysis in acute clinical settings where patient cooperation may be restricted **(38)**.

Exercise electrocardiographic stress testing

After its introduction almost a century ago, formal exercise testing has evolved into one of the most widely employed noninvasive methods for assessment of the clinical and physiologic status of the heart and circulatory system. The extensive and vital information obtained during standard exercise electrocardiography (EECG) includes symptoms, functional capacity (FC) and the responses of heart rate (HR), blood pressure (BP), and electrocardiogram (ECG), as well as unique non-ECG features (functional capacity [FC], heart rate recovery [HRR]) of significance for diagnosis, prognosis, and management of cardiovascular disease (CVD) **(39)**.

Indications for Exercise Testing

There are numerous indications for EECG, of which the detection of exercise- induced myocardial ischemia, and thereby likelihood of CAD, is the most frequent. Symptoms of CVD are wide-ranging and varied, and for many of these, there is a role for EECG in ascertaining clinical impairment and evidence of the underlying condition. Relatively common indications for EECG, in addition to chest pain, include dyspnea, palpitations, fatigue, and syncope. EECG also has an important role in prognosis and management of established CVD. This noninvasive method can unmask symptoms of CVD and their thresholds, estimate extent of disability from estimated functional capacity, provide prognostic data, assess efficacy of medical and interventional therapy, and indicate the basis for an exercise prescription **(40)**.

In patients with established CAD, valvular disease, cardiomyopathy, or congenital heart disease, EECG offers quantitative data to help monitor disease course and the timing of interventional therapy based on both its ECG and non-ECG data. However, the application of EECG in healthy, asymptomatic individuals has been a continuing concern because of the high rate of false positive tests in this population. Therefore, there should be specific indications for EECG in asymptomatic persons, such as a high coronary risk profile and an early family history of CVD, or for sedentary middle-aged/elderly individuals prior to initiating an exercise program **(41)**.

Detection of exercise-induced myocardial ischemia

Among the multiple reasons for performing EECG, chest pain is the most frequent, typically to aid in the detection or exclusion of CAD by provocation of exercise- induced symptoms and/or signs of ischemia. A variety of exercise protocols are appropriate for differing patients' indications and estimated functional capacity **(42)**.

The initial stress test for evaluation of chest pain in low-risk patients has been EECG without imaging if the baseline ECG is normal, evaluation suggests that the subject can exercise adequately, and estimation of the site and size of an ischemic cardiac defect is not the goal. If the latter data are necessary, a stress imaging study is indicated **(43)**.

In healthy vessels, resistance is primarily determined by the microvascular network—mainly prearterioles (100–400 μm) and arterioles (<100 μm)—which dynamically adjusts coronary blood flow according to metabolic demand. When oxygen requirements rise, endothelial cells release vasodilators like nitric oxide that diffuse into vascular smooth muscle, activating soluble guanylyl cyclase, increasing cGMP, and causing smooth muscle relaxation. This endothelium-dependent mechanism enables a robust 3- to 5-fold increase in coronary blood flow under physiological stress by lowering microvascular resistance **(44)**.

Ischemia is most frequently detected by the lateral precordial leads (V5,6), likely related to their position on the chest in relation to the major mass of the left ventricle. Exercise-induced ST depression that is isolated to the inferior leads is associated with a high rate of false positive results that has been attributed to the effects of atrial repolarization on the ST segments in these leads. By contrast, the effect of atrial repolarization on the ST segments of the lateral leads is minimal **(43)**.

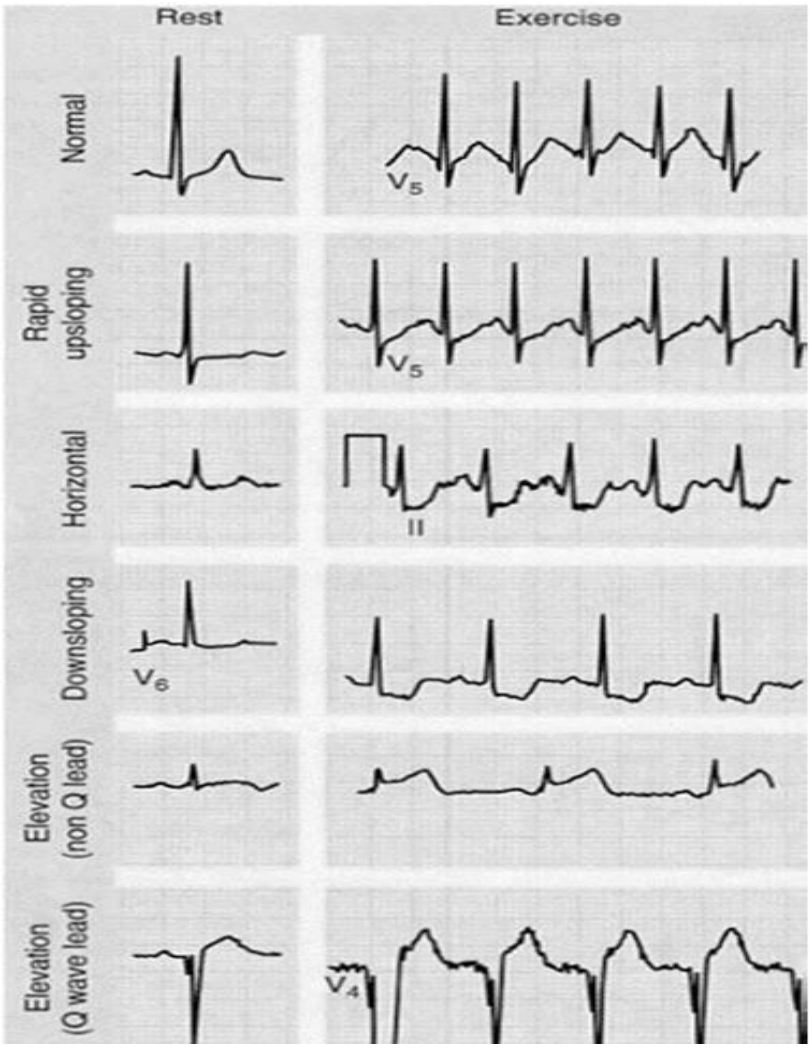

Figure 2: During exercise testing, ST-segment changes on ECG can indicate varying degrees of cardiac response. A normal resting ECG shows an isoelectric ST segment. "Rapid upsloping" ST depression is often seen and may be benign unless exceeding 3 mm, which suggests ischemia. "Downsloping" ST depression with >2 mm J-point depression and continued ST decline is more strongly associated with ischemia. Exercise-induced ST elevation in leads with or without Q waves can indicate coronary spasm or a previous infarction with wall motion abnormality, respectively. Interpretation relies on a normal baseline ST segment to detect pathological changes during stress **(45)**.

Exercise electrocardiography (EECG) has variable accuracy in detecting coronary artery disease (CAD) when compared to coronary angiography. Baseline ECG abnormalities, such as ST-segment depression or elevation, limit EECG's reliability for ischemia detection, making stress imaging tests preferable in these cases. Other factors affecting EECG performance include pre-test CAD probability, cardiac structural abnormalities, medication use, and referral bias—where angiography is more common in high-risk patients, artificially inflating sensitivity but lowering specificity **(46)**.

The extent of CAD significantly influences EECG results. Severe disease (e.g., left main or three-vessel CAD) is rarely missed, whereas single-vessel disease, especially in the right coronary or left circumflex arteries—often yields false negatives. Isolated left anterior descending CAD, however, is detected more reliably, with sensitivity exceeding 50%. Notably, patients with ischemic ST changes on EECG but good functional capacity (≥10 METs) tend to have a favorable prognosis, underscoring the importance of exercise tolerance as a key prognostic indicator beyond ECG findings alone **(47)**.

Exercise electrocardiography in women

Early exercise electrocardiography (EECG) studies in women showed higher false-positive rates for detecting coronary artery disease (CAD) compared to men, leading some clinicians to prefer stress imaging tests—such as nuclear or echocardiographic stress tests—as the initial diagnostic approach for women with chest pain. However, these imaging studies are more expensive and sometimes involve radiation exposure **(45)**.

The higher false-positive rates in women can be attributed to several factors, including the later onset of CAD in women (typically about a decade later than in men) and the inclusion of many premenopausal women in early EECG studies, where CAD prevalence was low. As women age, the false-positive rate decreases, aligning more closely with that of men. Bayesian principles explain this trend: when testing a population with a low likelihood of disease, even a moderately specific test will yield more false positives. Current guidelines for evaluating symptomatic women consider pretest risk, recommending EECG for low-to-intermediate-risk patients and reserving stress imaging for intermediate-to-high-risk cases **(45)**.

The Duke treadmill score (DTS), which integrates exercise duration, symptoms, and ECG changes, has proven useful for assessing both diagnosis and prognosis in men and women. A particular diagnostic challenge arises in patients—especially women—with evidence of myocardial ischemia despite nonobstructive CAD. While this condition is not benign, long-term follow-up data suggest that survival remains high (>95%) regardless of ischemia presence, contrasting sharply with the poorer outcomes seen in patients with prior myocardial infarction. Additionally, long-term monitoring of low-risk women presenting to the emergency department with chest pain (but no acute coronary syndrome) revealed no subsequent cardiac events over five years, reinforcing that not all ischemia detected by testing translates into adverse outcomes. This underscores the importance of risk stratification and selective use of advanced imaging in women with suspected CAD **(48)**.

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