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Role of Stress Electrocardiography in Ischemic Heart Disease and Non-Obstructive Coronary Disease

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Abstract:

Ischemic heart disease (IHD) remains the leading cause of morbidity and mortality worldwide. Stress electrocardiography (ECG) or exercise treadmill testing is one of the most established, non-invasive diagnostic tools for detecting myocardial ischemia. It provides valuable information regarding functional capacity, hemodynamic response, and electrocardiographic changes suggestive of ischemia. Despite the emergence of advanced imaging modalities, such as stress echocardiography and coronary computed tomography angiography (CCTA), stress ECG continues to serve as a first-line investigation, especially for patients with intermediate pre-test probability of coronary artery disease (CAD).

Keywords: Stress electrocardiography; Ischemic heart disease; Exercise treadmill test; ST-segment depression; Coronary artery disease; Duke Treadmill Score.

Introduction:

Ischemic heart disease (IHD) remains the leading cause of morbidity and mortality worldwide, contributing to nearly one-third of all global deaths each year. It results from an imbalance between myocardial oxygen supply and demand, most often due to atherosclerotic narrowing of the coronary arteries. Early and accurate detection of ischemia is therefore essential for timely management and prevention of adverse cardiac outcomes **(1).**

Stress electrocardiography (ECG) or exercise treadmill testing continues to be one of the most accessible and cost-effective diagnostic modalities for evaluating patients with suspected IHD. It provides valuable data regarding exercise capacity, hemodynamic response, and ischemic changes in the ST segment during graded physical exertion. Despite newer imaging modalities, stress ECG remains a first-line investigation in patients with intermediate pre-test probability of coronary artery disease (CAD) who can exercise and have an interpretable baseline ECG **(2).**

In addition to its diagnostic role, stress ECG carries significant prognostic importance. Parameters such as exercise duration, maximum heart rate achieved, and rate of heart rate recovery are strong predictors of long-term cardiovascular risk. When interpreted with clinical context and risk scoring systems such as the Duke Treadmill Score, stress ECG provides robust information for risk stratification and follow-up of patients with stable ischemic heart disease **(3).**

Although stress ECG (sECG) is recommended as an initial test for evaluation of patients with chest pain and intermediate likelihood of CAD, it is less and less used as a stand-alone test. This is likely due to multiple reasons some of which have been alluded to earlier: limited sensitivity and specificity, false positives and the ready availability of more sensitive imaging modalities for detection and localization of ischemia such as SPECT, stress echocardiography (SE) and coronary computed tomography (CCTA). Perfusion abnormalities, diastolic dysfunction and wall motion abnormalities all precede sECG changes in the ischemic cascade **(4).**

Various stress imaging modalities were used and hence identify these earlier imaging signs of ischemia, the sensitivity of detecting true subendocardial ischemia with SE) or flow heterogeneity (SPECT or PET) increases albeit with some loss of specificity particularly when dealing with perfusion imaging. As ruling out

significant CAD is the primary aim for ischemia based testing, the paradigm has shifted accordingly to incorporating SPECT or echocardiography with sECG to enhance sensitivity and to localize ischemia better. This combination of sECG and imaging provides the clinician a wealth of information to better risk stratifying individuals into low, intermediate, and high risk categories. There is substantial accumulated evidence that SPECT perfusion can reclassify patients in low, intermediate, and high risk sECG categories as determined by the DTS (**5**).

Although prior studies using sECG echocardiography have suggested that patients with sECG changes suggestive of ischemia and normal stress echocardiogram have long-term favorable outcomes, more recent studies have suggested that these patients may still be at slightly higher risk. Hence to some extent this study appears to reemphasize the prognostic value of sECG changes in absence of imaging evidence for ischemia. It is possible that abnormal sECG maybe more reflective of endothelial dysfunction rather than obstructive CAD in this discordant setting, in contrast to echocardiography, which is a better marker of obstructive CAD as it primarily evaluates wall motion abnormalities related to ischemia (**6).**

Specific indications do still exist where sECG alone is used outside of CAD evaluation such as assessing exercise capacity and exercise hemodynamics in asymptomatic valvular heart disease, evaluation of palpitations, for exercise induced arrhythmias and pre-cardiac rehabilitation or exercise program assessment for exercise prescription. Specifically, sECG continues to be recommended in 2020 American College of Cardiology/American Heart Association valvular heart disease guidelines specifically in asymptomatic aortic stenosis assessment and in combination with echocardiography for assessment of mitral valve stenosis and regurgitation for clarification of hemodynamic response and impact of valve disease on exercise parameters along with symptom correlation (**7).**

sECG has also been part of major clinical trials evaluating ischemia. As discussed earlier, the WOMEN trial randomized symptomatic women to sECG versus SPECT and showed no differences in outcomes at 2 years along with higher cost and exposure to radiation with use of SPECT. This trial questioned the common notion among physicians that sECG may not be ideal as an initial diagnostic test in women due to higher false positive response. Furthermore, with no radiation and a high negative predictive value, it serves as a safe low cost option to assess symptomatic women particularly in the low-intermediate risk category (**8).**

In a retrospective registry comparing the complementary value of sECG and CCTA, 582 patients underwent both tests. This study showed that in patients with low to intermediate risk sECG based on DTS, despite the presence of non-obstructive atherosclerosis on CCTA, sECG retained its prognostic value whereas in higher risk sECG (DTS <5), CCTA provided the most prognostic information. Similarly, sECG was also used as part of PROMISE trial, which evaluated functional testing (10% of randomized patients to functional testing had sECG) versus CCTA and showed no difference between these two strategies in initial approach to evaluation of suspected coronary disease (**9).**

Diagnostic and Prognostic Value of Exercise ST Changes

A meta-analysis of 24,047 patients in 147 studies found ExECG to have a pooled sensitivity of 68% and specificity of 77% for detection of CAD. Restricting the analysis to the 3 studies free of workup bias lowered sensitivity considerably to 50% and increased the specificity to 90%. ExECG has a positive likelihood ratio (LR) of 2.18 and a negative LR of 0.32 for CAD. Confounders such as resting ST-depression, digoxin usage, and left ventricular hypertrophy with repolarization changes decrease specificity, while mild single vessel disease decreases sensitivity. Despite these confounders, ExECG is still considered diagnostic in most patients able to reach 85% of their maximum age-predicted heart rate (**10).**

Exercise-induced ST depression is also a powerful predictor of cardiac events. Two landmark studies of large, predominately male populations, found the presence and extent of ST depression to be a powerful prognostic marker. In the Duke study of 2,842 patients, the maximum ST deviation was the strongest predictor of both cardiac death and a composite of cardiac death and nonfatal MI (**11).**

Additional Tools to Increase Diagnostic and Prognostic Utility

Exercise Capacity

There are many additional variables that supplement ST depression and add to the diagnostic and prognostic utility of ExECG. The most powerful of these is exercise capacity. Multiple studies have correlated exercise workload to the likelihood of significant myocardial ischemia on MPI and subsequent events. **Bourque et al. (12**) found that patients attaining <7 METS had an 18-fold higher prevalence of substantial (≥10%) left ventricular (LV) ischemia compared with those reaching ≥10 METS. The latter group with good exercise tolerance had a very low (0.4%) prevalence of ≥10% LV ischemia. A follow-up analysis of the cohort reaching ≥10-METS revealed very low rates of cardiac death (0.1%/year) and nonfatal MI (0.7%/year). The favorable diagnostic and prognostic impact of achieving a high exercise workload has been confirmed in multiple subsequent studies, including a Canadian cohort of 9,605 patients, and an analysis using patients who underwent exercise echocardiography (**13).**

Stress Electrocardiographic Findings Beyond ST Depression

Markers other than exercise-induced ST depression have diagnostic and prognostic value, such as the rapidity of recovery of ST segment changes. Christman et al. found a low 2% rate of positive imaging or findings of CAD on angiography and a 0.7% rate of a composite endpoint of cardiovascular death, nonfatal MI, or coronary revascularization in patients with a positive exercise treadmill test but rapid ST segment recovery. Other potential enhancements to the standard dichotomous presence of ≥1mm ST depression include heart rate adjustment in the form of the ST/HR slope and ST/HR index (**14).**

Lead AVR is often neglected in ExECG interpretation but has unique vector positioning. This allows it to function as a "pseudo-intracavitary" lead that may identify anterior wall transmural ischemia. Uthamalingam et al. found ≥1mm AVR elevation during ExECG to be the strongest predictor of an obstructive left main or ostial left anterior descending (LAD) artery stenosis with a diagnostic accuracy of 80% and a 2.6-fold increase in post-test probability. A major limitation of the current AVR data is the absence of studies examining imaging findings and events in the general population not undergoing invasive angiography **(15).**

Other suggested measurements on standard ExECG that may have diagnostic value include changes in QRS duration, R-wave amplitude, and length of the rate adjusted QT-interval. A novel marker not routinely available but with substantial potential as a useful adjunct to ST depression is high-frequency mid-QRS (HF-QRS) analysis, an interrogation of the signal in the 150-250 Hz frequency. An abnormal HF-QRS signal increases the sensitivity of ischemia detection from 39% to 69% ($p<0.005$) and the specificity from 82% to 86% ($p<0.05$). This promising tool requires additional validation in independent cohorts and with assessment of cardiac events before it can be routinely applied in clinical practice (**16**).

Physiologic Markers and Symptoms

Several physiologic markers during stress testing can augment the diagnostic accuracy of ExECG and have prognostic importance. These includes the heart rate and blood pressure responses to exercise, and symptoms during testing (**11).**

An impaired chronotropic response has been associated with a >2-fold increase in perfusion defects and a higher risk of CAD and cardiac events. Heart rate recovery post-exercise also carries significant diagnostic and prognostic power. Cole et al. found a relative risk of death of 2.0 (1.5-2.7, $p<0.001$) for those with a <12 bpm heart rate drop 1 minute post-exercise after risk-factor adjustment in 2,428 patients. A retrospective analysis of 2,193 men found a heart rate recovery <22bpm at 2 minutes to be predictive of mortality and the presence of CAD. Heart rate recovery retains its prognostic influence in patients with known CAD (**17).**

Changes in blood pressure response during ExECG are also potential indicators of CAD, although less validated than changes in heart rate. The systolic blood pressure (SBP) typically decreases at least 15% by 3 minutes post-exercise. An abnormal SBP recovery ratio of >0.9 (SBP at 3 minutes/SBP at peak exercise) has been found to have comparable diagnostic accuracy to ST depression and incremental value for the identification of

CAD. This same ratio correlates with the extent and severity of thallium-201 perfusion defects. A >10mmHg SBP drop during exercise and a delayed decline in SBP after exercise have been associated with high-risk multi-vessel or left main disease in men with less specificity in women (**11).**

Treadmill-induced typical angina increases the sensitivity for the diagnosis of CAD and indicates more extensive myocardial ischemia and higher event rates, particularly in the setting of ischemic ST depression. The risk of events is substantially higher when symptoms are induced at a lower workload (**18).**

Baseline ECG Abnormalities

Several baseline ECG abnormalities affect the test characteristics of ExECG. In a cohort of 1,282 patients referred for chest pain evaluation, resting ST depression <1mm increased the sensitivity of ExECG from 45% to 77% but decreased specificity from 84% to 48% with no change in overall diagnostic accuracy. Patients with left bundle-branch block (LBBB) require imaging due to a high false-positive rate. The role of ExECG in the setting of right bundle-branch block (RBBB) is less clear. ST changes in the anterior precordial leads have a false-positive rate of 66%, but specificity is preserved in leads V5 and V6. A study found a decreased sensitivity of 27% but a preserved specificity of 87% using leads V5 and V6 in 133 patients, the largest cohort studied with RBBB. A study, on the other hand, showed an excellent sensitivity of 89%, though only 12 patients were analyzed. The ACC-AHA exercise testing guidelines support the use of ExECG in RBBB (**11).**

Importance of Reaching ≥85% Maximum Age-Predicted Heart Rate

Given the late occurrence of ECG changes in the ischemic cascade and known limited sensitivity of ExECG, reaching an adequate level of workload and heart rate is essential. Heller et al. found that reaching only 70% compared with ≥85% of maximum age-predicted heart rate (MAPHR), leads to a reduction in the incidence of stress defects from 100% to 47% and a reduction in angina from 84% to 26%. Subsequent studies in patients not achieving target heart rates have found reductions in the degree and extent of ischemia on MPI, with decreases seen irrespective of the number of diseased vessels. Combination protocols with vasodilator administration in those unable to achieve sufficient exercise workload substantially improve the diagnosis of ischemia and are safe and feasible. In one study of symptomatic patients, receiving a combination protocol increased ischemic segments from 7 to 40 (**19).**

Patient-Centered Approach to Ischemia Evaluation

Advances in imaging technology have created a broad menu of options for the evaluation of ischemic heart disease that facilitate a patient-centered approach to ischemia evaluation. Patient symptoms, comorbidities, and functional status are used to identify which array of appropriate tests are considered. Patients are referred for the test that provides the most clinically meaningful information with the least risk, cost, and inconvenience (**20).**

In many patients, adequate risk stratification is achieved with a simple strategy of ExECG without imaging. A study of the yield of downstream testing and subsequent cardiac events in 3,656 patients undergoing ExECG found low rates of referral to MPI (9.0%) and invasive angiography (2.3%). Over a 2.5-year mean follow-up, the rate of cardiac death, nonfatal MI, and coronary revascularization was very low in those with negative (0.2%) and inconclusive (1.3%) stress studies. A large administrative database found a similarly low 6.9% rate of invasive angiography at one year. In the functional testing subgroup of the PROMISE trial, those who underwent stress electrocardiography had a similarly low rate of the combined endpoint of adverse cardiac outcomes as those who underwent imaging. These data support an initial strategy of ExECG alone in appropriate patients (**14**).

Stress myocardial perfusion imaging (MPI) provides minimal incremental value in patients with a low-risk exercise stress test, a low-risk Duke Treadmill Score, or a high rate-pressure product without ST-segment depression. In addition, the low cardiac event rates in stable patients treated medically in landmark studies such as COURAGE and BARI-2D have challenged the paradigm of selecting coronary revascularization as the initial therapeutic strategy, potentially reducing the need for identification of low-levels of ischemia. However, despite the low risk of events with negative ExECG, there continues to be widespread use of concurrent imaging. Novel protocols that add additional testing in specific higher risk situations may encourage a strategy of ExECG alone **(21).**

Is treadmill testing ready for its swan song or can resurrect its role in CAD?

Given the explosion of various imaging modalities, both functional and anatomic for noninvasive imaging of CAD, the sECG test has come under intense scrutiny given its limited sensitivity and specificity. The United Kingdom National Institute of Clinical Excellence (NICE) 2010 recommendations deemphasized sECG testing given its limited incremental prognostic value over clinical assessment, and in 2010 recommendations in 2016, NICE recommended CCTA as first-line testing for chest pain and removed traditional Bayesian based pre-test likelihood assessment strategy arguing its inaccuracy and overestimation of CAD likelihood. This represented a major shift in approach to suspected chest pain and diagnostic workup for CAD in the United Kingdom. The European Society of Cardiology on the other hand continues to recommend pre-test likelihood assessment but no longer recommends using sECG as a test to assess CAD, quoting low sensitivity. In contrast the American College of Cardiology and American Heart Association continue to recommend sECG in intermediate pre-test likelihood and ability to exercise (**22).**

In the most recent 2021 ACC/AHA chest pain guidelines, pre-test likelihood estimates are still recommended and in intermediate risk chest pain patients with no prior CAD, sECG still receives a Class 1 indication along with all other stress imaging modalities for evaluation (**23).**

The Achilles heel for sECG remains its low-average sensitivity and specificity along with lack of localization and extent of ischemia. This has served as the major driver for its declining popularity compared to other stress imaging modalities. Stress imaging on the other hand despite combining exercise in some of its protocols still can evaluate for only moderate-severe CAD in most cases as the crux of all stress tests is to evaluate coronary flow reserve limitations which remains intact in mild-moderate CAD. Hence a substantial portion of early atherosclerosis (mild-moderate non-obstructive plaque) remains undetected, as ECG response, perfusion and wall motion are usually preserved in early CAD. This scenario represents a missed opportunity not only for early detection of atherosclerosis but also for non-initiation of preventive lifestyle strategies and statin therapy initiation. Thus, techniques like coronary calcium score and CCTA whose strength lies in detection of any degree of atherosclerosis have been able to fill this gap by detection of atherosclerosis spanning the entire spectrum of non-obstructive to obstructive CAD. This was illustrated in the SCOT-HEART trial which showed that CCTA strategy impacted outcomes with reduction in MI likely from more implementation of preventive strategies like statins once any atherosclerosis is detected (**5).**

The much awaited 2021 ACC/AHA chest pain guidelines has now acknowledged the growing diagnostic and prognostic value of atherosclerosis detection by given CCTA a Class 1 (level A) recommendation with adjunct use of fractional flow reserve by CT (FFRCT) as an initial test of choice in patients presenting with chest pain and suspected CAD. This in a way provides a combination of atherosclerotic plaque delineation and when indicated a functional assessment of detected disease with FFRCT or even better with sECG which can provide a wealth of functional information (**23).**

An important limitation of CCTA ± FFRCT is that it can only evaluate epicardial CAD. The spectrum of CAD spans into the micro-circulation with many patients having angina or ischemia without obstructive CAD (ANOCA or INOCA). These can only be evaluated by functional testing and not simulated hyperemia using FFRCT. Keeping cost and radiation exposure in mind when doing multiple tests, one could envision using routine calcium scoring for detection of atherosclerosis and treadmill testing for ischemia assessment as a simple yet effective initial strategy for workup of chest pain and suspected CAD. This concept is not entirely new and was proposed almost 8 years ago as a low risk option of combining anatomic and functional information for diagnosis and prognosis of CAD (**24).**

Although calcium score is well established to prognosticate in asymptomatic atherosclerosis, its role in predicting inducible ischemia has also been studied. Many studies have shown that the incidence of ischemia on functional studies (mainly SPECT) increase with increasing burden of calcium. These data have led to appropriate use criteria for SPECT imaging to incorporate recommendations for selective use of SPECT in patients with calcium score ≥400 as most studies show increasing likelihood of ischemia at or beyond this level of calcium score **(25).**

On the other hand, calcium score <100 is associated with very low inducible ischemia and could be used as a gatekeeper to avoid further testing. Thus, calcium score with a functional study such as sECG (referred to as 'calcium treadmill test') provides atherosclerosis information plus key physiologic data points, namely functional capacity, arrhythmia detection, hemodynamic response to exercise and electrocardiographic ischemia. A completely normal calcium treadmill test can help reassure both patient and clinician of low cardiovascular risk warranting only lifestyle and preventative medical therapy. An abnormal calcium treadmill test will require further decision making regarding need for further advanced imaging (CCTA or stress imaging) versus cardiac catheterization based on patient symptoms and extent of abnormalities. This step wise approach can be more easily implemented rather than routinely performing SPECT/PET or CCTA, which is costlier and/or expose patients to higher radiation burden. The radiation from calcium score scan is minimal, mostly less than 2 milliseiverts, which is an acceptable tradeoff for the wealth of diagnostic and prognostic information for the patient. Also as recent studies such as ISCHEMIA have not shown a clear benefit of routinely intervening even with moderate-severe ischemia, one could just adopt a trial of aggressive medical therapy even when calcium treadmill test is abnormal if patient is asymptomatic or minimally symptomatic **(26).**

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