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## Review Article

## Stress electrocardiography testing in coronary artery disease: Is it time for its swan song or to redefine its role in the modern era ?

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## ABSTRACT

Stress electrocardiography (sECG) or treadmill stress testing is a well validated noninvasive diagnostic modality available to clinicians at low cost yet providing valuable functional data for coronary artery disease (CAD) diagnostic and prognostic evaluation. With the advances in cardiac imaging in both functional and anatomic fronts and the existing limitations of sECG testing, this modality appears less favored worldwide as reflected in some recent guideline updates. We review the past present and future of sECG to provide a viewpoint on where it stands in CAD evaluation and if it will remain relevant as a diagnostic modality or be retired going forward. We also provide our perspectives on how sECG can co-exist with other modalities such as calcium scoring and discuss the role of such testing in the Indian population.

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## 1. Introduction and historical perspective

Fiel and Seigel in 1928 are probably credited with the first description of ST and T wave changes on electrocardiography (ECG) in patients during chest pain subjected to repeated sitting and standing with demonstration of subsequent regression of these changes with cessation of exercise or administration of nitroglycerin<sup>1</sup> Subsequent multiple other publications including that of Misael<sup>2</sup> and Masters et al<sup>3</sup> documented the same phenomenon ushering in the era of stress electrocardiography (sECG). The introduction of the Bruce protocol in 1956<sup>4</sup> established the methodologies of stress protocols upon which many subsequent modifications of stress testing protocols emerged. In the 1970s, the concept of Bayesian analysis to evaluate pre-test likelihood of coronary artery disease (CAD) to help guide choice of appropriate patients for noninvasive testing was introduced and adopted widely in guidelines for stress testing.<sup>5</sup> The 1980s saw the evolution of sECG testing to incorporate imaging with radionuclide

myocardial perfusion imaging ie single-photon emission computerized tomography (SPECT)) to increase sensitivity of detection of CAD, albeit with radiation exposure<sup>6</sup> followed by sECG with echocardiography in the 1990s which continues to be widely adopted to the present day.

For the purposes of this review we will divide the era of sECG into past (1970–2005), present (2005–2020) and future (2021 and beyond) to highlight the changing landscape of assessment and prognosis of CAD and if sECG will continue to withstand the competition from advanced CAD imaging or sing its “swan song.”

## 2. The past

Diagnostic and prognostic testing of CAD with sECG has been widely established and often used as the first step in evaluation of chest pain. sECG has also been used extensively to assess functional capacity, evaluate for arrhythmias, monitor effects of medical therapy and provide exercise prescription for those wanting to engage in physical activity. It has established itself since its inception as an inexpensive, widely available, safe and easy to perform initial test for many decades. The 2002 American College of Cardiology updated guidelines on sECG and the 2005 American Heart Association guidelines for testing in women both recommended sECG as first line for evaluation of suspected CAD in intermediate

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pre-test likelihood patients with normal or near normal resting ECG.<sup>7,8</sup> The diagnostic value of sECG for CAD detection using standard ST-segment depression criteria (1-mm horizontal depression at 60–80 ms from J point<sup>9</sup>) has enjoyed variable success in men and women. In a meta-analysis of mostly male subjects, sensitivity was reported as 81% and specificity 66%.<sup>10</sup> However, sensitivity as low as 45% and specificity around 85% have also been reported when “work up or referral bias” was accounted for. The diagnostic value of ST depression in women is much less than men with sensitivity of 61% and specificity 70%<sup>11</sup> and in another study, positive predictive value of ischemic ST depression compared to coronary angiography was much lower compared to men (47% vs 77%,  $p < 0.05$ )<sup>12</sup> Although the exact reasons for this lower predictive value or higher “false positive” rate in women is unclear, some factors attributed to this phenomenon include greater baseline ST changes in women, estrogen based digoxin like ST-segment effect and timing of testing related to menstrual cycle.

Prognostically, ST-segment depression and exercise capacity has been the cornerstone for predicting outcomes for many decades. In a predominantly male database from the Duke Cardiovascular Data Bank, the presence of 1-mm ST depression within the first 2 stages of Bruce protocol was associated with worse outcomes.<sup>13</sup> On the contrary those achieving 10 metabolic equivalents or more on the Bruce protocol had a low risk of cardiac events regardless of presence or absence of ST depression.<sup>14</sup> The prognostic value of ST depression in symptomatic women was evaluated in the What Is the Optimal Method of Ischemia Evaluation in Women Trial (WOMEN), which compared sECG to sECG + SPECT and showed no differences in outcomes.<sup>15</sup> Furthermore ST depression had no prognostic value in asymptomatic women in another study.<sup>16</sup> The ability to exercise at least 2 stages of the Bruce protocol and achieve 6 metabolic equivalents has been shown to be associated with lower risk of cardiovascular events. In a study of CAD diagnosis using sECG and SPECT, those who achieved 10 metabolic equivalents or more had a 0% prevalence of significant ischemia on SPECT.<sup>17</sup> One of the widely used parameters in sECG prognosis is the Duke treadmill score (DTS), which factors in exercise time, maximum ST depression and presence of angina during test. Those with a DTS of 5 or above had excellent 5-year prognosis whereas those with a DTS worse than –11 had poor outcomes.<sup>18</sup> The complementary role of SPECT with DTS has been shown with its ability to further risk stratify patients with intermediate DTS into lower or higher risk based on presence or absence of ischemia.<sup>19</sup>

Too often clinicians focus only on ischemia criteria and look for “yes” or “no” answer in a sECG study. Many other important parameters are available in sECG study but unfortunately are not widely appreciated or weighted as part of study interpretation. These include blood pressure and heart rate response, heart rate recovery and presence of exercise induced arrhythmias all of which add value to the sECG mainly from prognostic standpoint. The ability to augment systolic blood pressure during sECG has been shown to be inversely correlated to angiographic CAD. An exaggerated or hypertensive response (systolic blood pressure  $>210$  mm Hg and  $>190$  mm Hg in women) in young adults was shown to be a future predictor for hypertension<sup>20</sup> whereas a fall in systolic blood pressure ( $\geq 10$  mm Hg) or delayed recovery of blood pressure in recovery phase was associated with left main or severe CAD.<sup>21</sup> Chronotropic response is key to adequate diagnostic accuracy of sECG and an integral part of sECG prognostic value. In general achieving  $\geq 85\%$  predicted maximum heart rate ( $220 - \text{age} \times 0.85$ ) has been used as adequate chronotropic response. However, the predicted maximal heart rate for women has been redefined as  $206 - 0.88 \times \text{age}$  based on the St. James Women Take Heart study.<sup>22</sup> Chronotropic incompetence or inability to achieve adequate heart rate has been associated with adverse long-term outcomes and

related parameters such as heart rate reserve (peak – rest heart rate) and chronotropic index (heart rate reserve/metabolic reserve) have all been shown to have prognostic implications.<sup>23–25</sup> In particular a chronotropic index of  $<0.80$  (normal being 1) is associated with adverse long-term outcomes.<sup>25</sup>

### 3. Present

Although sECG is recommended as an initial test for evaluation of patients with chest pain and intermediate likelihood of CAD,<sup>26,27</sup> it is less and less used as a stand-alone test in the United States currently. 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 most recently over the last 15 years, coronary computed tomography (CCTA). Perfusion abnormalities, diastolic dysfunction and wall motion abnormalities all precede sECG changes in the ischemic cascade. As we use various stress imaging modalities 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.<sup>19</sup> Although prior studies from our group using sECG echocardiography have suggested that patients with sECG changes suggestive of ischemia and normal stress echocardiogram have long-term favorable outcomes,<sup>28</sup> 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.<sup>29</sup> 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.<sup>30</sup>

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.<sup>31</sup>

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.<sup>15</sup> 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.<sup>32</sup> In a more recent trial of 9849 patients with chest pain (SCOT-HEART trial), of whom 4146 were ultimately randomized, 85% of patients underwent sECG and then were randomized to CCTA versus standard of care.<sup>33</sup> In this trial, CCTA increased the frequency of cardiac catheterizations but did clarify initial diagnosis of angina as CAD or not more often than sECG. After 1.7 years of follow-up, CCTA was associated with a lower incidence of myocardial infarctions. There was no difference in revascularization between both groups. This trial set the stage for a contemporary direct comparison between a single common test, such as sECG versus sECG + CTCA, as a new paradigm and clearly showed that addition of an anatomic to a functional study increases implementation of preventive therapies, such as statins and antianginal therapies, compared to standard of care. This most likely is related to a more correct diagnosis of CAD in the CCTA group. The decrease in myocardial infarction was likely driven by preventative therapy instituted as part of atherosclerosis diagnosis by CCTA. These findings has now been again confirmed in the five year extension data of SCOT-HEART.

#### 4. Future

##### 4.1. Is treadmill testing ready for its swan song or can we 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,<sup>34</sup> and in its most recent update of 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.<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup> This highlights that the divide in medical opinion on value of sECG still very much exists amongst major societal recommendations. So, how do we reconcile with these conflicting recommendations? Has the time really come for the sECG test to sing its swan song? or should it evolve to be part of CAD diagnostic testing ?

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. The much awaited 2021 ACC/AHA chest pain guidelines<sup>37</sup> 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. An important limitation of CCTA ± FFRCT is that it can only evaluate epicardial CAD. The spectrum of CAD as we now understand 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 we do 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.<sup>38</sup> 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.<sup>39,40</sup> These data have led to appropriate use criteria for SPECT imaging to incorporate recommendations for selective use of SPECT in patients with calcium score  $\geq 400$  as most studies show increasing likelihood of ischemia at or beyond this level of calcium score.<sup>41</sup> 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<sup>42</sup> 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.

### 5. The backdrop of cardiovascular disease in India and our perspective for the adoption of “calcium treadmill test “in India

The enormous increase in cardiovascular disease burden (CVD) in India is now well recognized and it is the leading cause of mortality. In 2016 the estimated prevalence of CVD in India was 54.5 million.<sup>43</sup> One in 4 deaths in India are due to CVD with CAD and stroke contributing >80%. To fuel this CVD problem is the fact that India has unfortunately gained the distinction of being dubbed “diabetes capital of the world” with a projected estimate of 79.4 million people expected to have diabetes by 2030. Diabetes affects macro and microcirculation and being the leading cause of CAD, sets the stage of diffuse atherosclerosis which spans epicardial arteries to microcirculation. Although data regarding national utilization of various stress testing modalities in India is lacking, sECG remains probably the most widely used test given its advantages of being readily available, affordable cost and low risk. Thus its applicability to the Indian population many of whom do not have insurance coverage is attractive for hospitals and cardiology practices. At the same time most private and government hospitals in India likely now have access to a reasonably state of art CT scanner being used for multiple purposes. Thus incorporation of calcium scoring program could be easily implemented for risk assessment. Hence ‘calcium treadmill test’ can then be thus instituted and requires minimum upfront costs to set up in Indian hospitals given readily available resources. The approach to patient selection could be on 2 fronts: 1) asymptomatic risk assessment (starting with calcium score and risks stratifying as discussed before with sECG as needed) versus 2) symptomatic assessment (starting with sECG and adding further risk assessment with calcium score which may be helpful to adjudicate borderline or mildly abnormal sECG).

For the majority of Indians who pay out of pocket for medical costs, the “calcium treadmill test” will definitely be more palatable than a costly CCTA or stress imaging test. Furthermore, a widespread adoption of this strategy will set the stage for earlier institution of preventative therapies like statins, low dose aspirin, lifestyle counselling inclusion smoking cessation, exercise and weight loss. Patients are more convinced for the need for risk reduction when they see coronary calcification and its implications rather than a stress test alone so the “combo” may be even more powerful for medical advice. We would like to highlight that starting with a calcium score could also prevents asymptomatic patients from routinely undergo CCTA or stress testing which unnecessarily creates a cascade of additional tests for findings which may or may not be clinically significant.

### 6. Conclusion

sECG is a widely studied, well validated, low-cost, low-risk technique for evaluation and prognostication for CAD. It is also currently used for exercise prescription, functional capacity, dyspnea assessment (in conjunction with oxygen consumption assessment), objective assessment of symptoms and stress

hemodynamics for valvular disease assessment. However in the current era, its use continues to decline given various advances in imaging as outlined above. An ideal strategy would be to consider the hybrid strategy of ‘calcium treadmill test’ to serve as gatekeeper for diagnosis and prognosis of CAD. This could be a cost effective initial approach to suspected CAD diagnostic evaluation particularly in India. sECG in our opinion is alive and well and is not ready for its “swan song.”

### Declaration of competing interest

No conflicts of interest for any authors in this manuscript. There is no funding sources to declare for this manuscript.

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