



## Original Work

### Clinical implications of ST segment time-course recovery patterns during the exercise stress test

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**ABSTRACT:** The exercise stress test (EST) is the commonest non-invasive test to elucidate the nature of chest pain/discomfort. ST segment depression provides evidence of ischemia, but is hampered by a significant number of false negative and false positive tests. This study evaluated patterns and duration of ST depression in an attempt to differentiate false positive and false negative tests. One hundred consecutive patients with suspected angina referred to the Cardiac Clinic, who underwent an EST, and subsequently a coronary angiogram, were studied. The EST was classified as positive if significant ST depression (greater than 1mm 80msec after the J point) developed during exercise or the recovery phase. Based on the angiographic findings as the reference, the EST was classified as true positive (TP), true negative (TN), false positive (FP) or false negative (FN). Onset, magnitude and type of ST depression in relation to disease, the recovery time (RT), total ischemic time (TIT) and time-course patterns in TP versus FP results were compared by Chi square test. The EST was positive in 77 patients (true positive n = 65; false positive n = 12). The angiographic findings were classified as normal (17), non-occlusive atheroma (10) and as significant coronary stenosis in the remainder. Though the mean time to ST recovery (IRT) was shorter (183 + 118sec) in subjects with false positive compared to true positive (264 + 116sec) p<0.05, it was over three minutes and did not really help in differentiating FP from TP tests. TIT was more reliable than the IRT in delineating true positive from false positive tests. Up-sloping ST changes were more commonly associated with false positivity. Time-course patterns could not reliably distinguish TP from FP tests (TIT = 8/12, RT = 7/12), but TIT was more reliable in verifying TP (64/65) tests than IRT (59/65).

**KEY WORDS:** *Exercise stress test; ST segment time course patterns*

#### INTRODUCTION

The diagnosis of angina is made on the grounds of typical pain and its relationship to effort and rest. Clinical assessment to determine whether chest pain is of ischemic origin (angina) is often ambiguous when a history of angina is difficult to ascertain, or when chest pain symptoms are atypical. Patients rarely present with all the typical features so that the diagnosis of angina is often in doubt and recourse to investigation becomes necessary in order to elucidate the nature of the chest pain / discomfort. Non-invasive tests are therefore important in validating angina, and in

quantifying the severity, as well as in the evaluation of atypical chest pain. In clinical practice the Exercise Stress Test (EST) remains the commonest non-invasive technique used to provide physiological evidence of myocardial ischemia. The most prominent and consistent response to ischemia in the electrocardiogram (ECG) during exercise is ST depression; however the wide variability in the pattern of ST changes and the significant rate of false positive and false negative findings demand that clear understanding of the ST segment changes appearing during stress is necessary for proper interpretation of the test result. In order to elucidate the clinical implications of the type and duration of ST changes this study was performed on one hundred consecutive patients admitted for angiography to the cardiac unit, Department of Cardiology, University of Kwazulu-

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Natal, Durban. The results of the exercise stress tests were compared to the coronary angiograms in an attempt to (a) describe the pattern of ST segment changes in patients with suspected angina, (b) determine the value of ST time course patterns during the recovery phase in differentiating a true from a false positive test and (c) establish a correlation (if any) between the persistence of depressed ST segments and the severity of coronary artery disease (CAD) on the angiogram.

## METHODOLOGY

The patients studied were referred to the cardiac clinic with a diagnosis of suspected angina. They were referred for the EST (standard Bruce protocol) and based on the clinician's decision, subsequently admitted for coronary angiography performed according to AHA guidelines<sup>1</sup>. Treadmill testing was performed using the Bruce protocol, with continuous monitoring of blood pressure, heart rate, and ECG up to ten minutes into recovery. The EST was classified as positive if significant (> 1mm) ST depression developed during the stress test or in the recovery phase after the treadmill was stopped. The test was stopped at target heart rate, if fatigue or if symptoms indicative of severe coronary disease developed (dizziness, angina or fall in BP > 20mmHg, or if the test became positive early (within 3 minutes) of initiating the EST). Data recorded included exercise time, maximum workload, blood pressure and heart rate, diagnostic change in ST segment, arrhythmias and reasons for stopping the stress test (limiting symptoms, ST segment depression of > 1mm 80msec after the J point, or achievement of target heart rate).

Patients with clinical evidence of significant ischemia underwent coronary angiography to confirm the severity of coronary stenosis and assess the suitability for revascularization. The angiographic finding was classified as clinically significant stenosis sufficient to cause angina if the percentage stenosis was greater than 50%. In the remaining cases the findings were classified normal or non-obstructive epicardial coronary disease. The severity of the disease was assessed according to (a) the number of vessels involved, (single, double and triple vessel disease) and (b) the percentage severity of stenosis (70%, 80%, 90%, 99% (subtotal) and total occlusion).

An individualized estimate of pretest probability (PPD) was based on estimates of the prevalence of disease by symptom, age and gender established by Diamond and Forrester<sup>2</sup>. The clinical features of the chest pain were defined as typical angina, atypical chest pain and non-anginal chest pain. The tables designed by Rifkin and Hood<sup>3</sup> were used to calculate the posttest probability.

In each patient the Duke Treadmill score<sup>4</sup> value was also calculated as follows: treadmill time (minutes Bruce Protocol) - (5 x magnitude ST-depression) - (4 x angina index), where 0 = no angina, 1 = non-limiting angina, 2 = limiting angina. Although this score is used to determine prognostic categories as follows: < -11 high risk, -10 to +4 intermediate risk, >5 low risk, the score was used as an index of disease severity for comparison with persistence of the ST changes during stress testing.

## Statistical analysis

Differences between variables were compared using simple descriptive statistics (mean  $\pm$  SD) and contingency tables. Two by two tables comparisons were used for calculation of Chi square (DF = 1) and the level of significance taken at  $p < 0.05$ . Angiographic findings were used as the gold standard with which to compare the results of the exercise stress test and the sensitivity and specificity determined. The parameters analysed were: the clinical features (chest pain, breathlessness) and demographics of the sample population, the onset of ST depression, the magnitude and type of ST segment depression in relation to disease, the time to ST segment recovery in relation to true positive (TP) test versus false positive (FP) test, the total duration of ST segment depression during exercise and recovery (total ischemic time (TIT)) of TP in relation to FP tests, the double product and analysis of time course recovery patterns in TP in relation to FP tests.

## RESULT

### Demographic Data And Clinical Characteristics

One hundred patients were studied (56 males and 44 females), of whom the majority (89%) were of Indian origin. The demographic data and clinical characteristics of the subjects are shown in **Table 1**. Smoking was more common in males (36% vs 8%) while risk factor clustering appeared more frequent in females (two or more risk factors 51% vs 31%).

Twenty patients manifested with chest pain during the test, and 14 patients of these had either single, double, or triple vessel disease. Breathlessness occurred in 66 patients, with angina pain occurring in only one patient. No patient in this study experienced hypotension or syncope, as the test was stopped when the patient complained of dizziness, which occurred in 14 patients. Eighty percent of patients with double and triple vessel disease had moderate to low (< 24000) double-product; this was attributed to prior treatment with beta blockers. In four of nine false negative tests, subjects were on beta blocker therapy.

The EST was positive in 77 patients (true positive n= 65; false positive n=12). No changes were documented during exercise or recovery in 23 subjects, yielding a test sensitivity of 89% and specificity of 56%. One patient with non-occlusive atheroma had changes in the recovery phase only. The angiographic findings were classified as normal (n=17), non-occlusive atheroma (n=10) and as significant coronary stenosis in the remaining 50 subjects. Global ischemia with reduced LV function was present in two patients, due to the presence of critical proximal left anterior descending artery stenosis.

**Table 1: Risk Profile of subjects undergoing stress tests**

Demographic data	Males n=%	Females n=%
Gender (%)	56	44
Indian	52	37
African	2	0
Caucasian	2	7
Age ( mean± SD)	50 ± 8.8yr	53 ± 9.8yr
History of smoking	36	8
Hyperlipidemia	34	22
Hypertension	32	23
Diabetes Mellitus	26	20
Prior MI	12	18
Family History	29	26
<b>Number of Risk Factors</b>		
0 Risk Factors	1	2
1 Risk Factor	3	12
2 Risk Factors	11	15
3 Risk Factors	12	16
> 3 Risk Factors	8	20

**Onset of ST Depression**

Twelve of the twenty-seven patients with normal or non-occlusive atheroma had false-positive tests. The onset of ST depression in nine of these patients occurred within three minutes. Two patients experienced ST depression after three minutes into the test and one patient had ST depression in the recovery phase only.

The onset of ST-depression in nine of the 23 patients with single vessel disease was less than 3 minutes; a further nine had onset of ST depression later than 3 minutes and 5 had false negative (FN) tests. Angiography showed that 3 of these FN

patients had significant proximal occlusion of the affected artery.

Seventeen patients with double vessel disease (DVD, n=23) had onset of ST-depression within 3 minutes. Two patients were false negative: the first patient had a significant (90%) stenosis in the proximal circumflex artery and diffuse narrowing of the right coronary artery (RCA), as well as a low double product (DP) of 18900, suggesting that this test was stopped prematurely. (METS = 4.8) The second patient had a 55% mid-left anterior descending (LAD) stenosis and a 60% stenosis in the posterior descending artery. The stenosis in these arteries were judged as not being severe. The remaining 4 patients had onset of ST depression later than 3 minutes.

The onset of ST depression in 18 of the 27 patients with triple vessel disease (TVD) occurred within 3 minutes into the exercise test. Eight patients had ST changes later than 3 minutes into exercise and 1 patient had a false negative test. This patient had significant stenosis of all 3 major arteries and exercised for 5 minutes. He also achieved a low DP of 19280 (METS = 5).

The depth of the ST depression indicated the likelihood of CAD: the predictive value of ST>3mm depression was 92% for CAD. We also studied the extent of the ST depression across the ECG leads during the test, which showed that extensive CAD is more likely to be present in patients who show substantial ST segment changes when it can be seen on multiple leads. Twenty patients had ST depression in <3 leads and fifty-seven patients had ST depression in >5 leads. The remaining 23 patients had no ST changes, as they comprised the FN and TN groups.

**Analysis of the ST segments at recovery**

*Type of ST depression*

The pattern of the ST-segment changes during recovery was horizontal depression in 46/77 patients, down-sloping in 21 patients and up-sloping in the remaining 10 patients.

Ten out of the 12 false positive tests exhibited up-sloping ST depression, suggesting that this pattern of up-sloping ST depression in a subject with a positive EST may be a marker for a false positive test. Amongst the 12 FP tests the time to recovery of the ST segment was variable: in 5 patients the recovery time was greater than 5 minutes; it was 4-5 minutes in 2 and less than 3 minutes in the remaining 5 subjects.

*Time to ST recovery*

The recovery time (ST depression to baseline) was less than 3 minutes in seven subjects with non-occlusive atheroma (FP) and in 9 patients with

single vessel disease. One patient with severe SVD (95% stenosis proximal LAD) had a prolonged recovery time of greater than 9 minutes. The ST segment in 21/23 patients with double vessel disease took longer than 3 minutes to recover to baseline; the remaining two patients had false negative tests.

Most (24/27) of the patients with triple vessel disease took longer than 3 minutes to return to baseline, with many of them (n=15) taking a recovery time of longer than 5 minutes. One patient had a false negative test, and the remaining two patients who had the recovery time of less than 3 minutes, had achieved a low level of METS of 4.8 and 3 respectively during the test, suggesting that these could have then been inadequate tests.

### Total Ischemic Time

Because of wide variability in the duration of the ESTs we tried to standardize the duration of the ischemic ST segment response by relating it to the total exercise duration. The total ischemic time (TIT), calculated as the time from the onset of the ST-segment depression during exercise, to the time it took to return to baseline in the recovery phase, was also indicative of the extent of disease. We found TIT to be better predictor of the accuracy of

the stress test (true negative or true positive) as assessed by angiography (**Table 2**).

### Post myocardial infarction Stress Tests

Twenty-three out of thirty patients who were exercised post-myocardial infarction showed ischemia on the ECG that was distant from the infarct territory. All patients had significant stenosis confirmed at angiography. The test was strongly positive (ST-depression > 2mm) in 14 patients. Of the seven negative tests three patients had non-occlusive atheroma at angiography (two had hypertension), and three had single vessel disease.

In an attempt to distinguish true positive from false positive tests we compared the total ischemic time (duration of ST depression during exercise and the recovery) with the time to recovery (Ischemic recovery time IRT) in our subjects. While we showed that the IRT time was shorter (183± 118sec) in subjects with false positive compared to true positive tests (264± 116sec) p<0.01, it was clear that the mean time to recovery was over three minutes and this parameter (time to recovery of ST segment depression) did not really help in differentiating these TP from FP tests (**Table 2**).

**Table 2: Classification of the Exercise Stress Test**

Clinical Parameter	Test Result				
	FP (n=12)	TP (n=65)	TN (n=15)	FN (n=8)	P-value
Age : ( $\bar{x} \pm SD$ ) (yr)	50.5 ± 10.5	52.4 ± 9.3	48 ± 8.9	46.5 ± 7.9	
Male/Female (n)	2 / 10	38 / 27	6 / 9	7 / 1	
Ejection Fraction (%)	62.5 ± 6	57.7 ± 10.5	63 ± 7.4	53.0 ± 9.2	
Beta-Blockers (%)	2 / 10	39 / 65	9 / 15	4 / 9	
Double Product (mean ± SD)	28713 ± 5005	22407 ± 5118	27471 ± 4108	22827 ± 5756	
Test duration (TET)(sec)	365 ± 77	360 ± 120	430 ± 163	481 ± 98	
Type of ST Depression: Horizontal/Up-/Down-sloping	3 / 9 / 0	40 / 1 / 24	-	-	
Onset of ST depression (sec)	225 ± 85	192 ± 90	-	-	
Time to Recovery ( IRT ) (sec)	183 ± 118	264 ± 116	-	-	P<0.01
Total ischemic time(TIT) (sec)	240 ± 102	430 ± 141	-	-	P<0.05
Exercise time (TET)	365 ± 77	360 ± 120	430 ± 163	481 ± 98	P=ns
TIT/TET ratio	0.9 ± 0.5	1.26 ± 0.6	-	-	P<0.05
Pre-test probability	56.2	79 ± 18	56.5 ± 22	74 ± 21.7	
Post-test probability	87	89.6 ± 9.3	56.5 ± 22	74 ± 21.7	

TIT: Total ischemic time during the exercise and recovery phases; TIT/TET: Ratio of total ischemic time to the test duration

Indeed what was evident from our results was that the total duration of ST segment depression (TIT) was more reliable (**Table 3**) than the ischemic recovery time in delineating true positive from false positive tests. ST depression that persisted into recovery, resulting in a prolonged ischemic time with a TIT/TET ratio >1, were indicative CAD. As mentioned above, up-sloping ST changes were more commonly associated with false positivity.

**Table 3: ST Depression in True vs False Positive Tests**

Parameter measured	P value
Ischemic Recovery Time (< 3 min): (TP vs FP)	P<0.01
Ischemic recovery time for SVD vs FP (< 3 min)	N/S
Ischemic recovery time for DVD vs FP (< 3 min)	P < 0.05
Ischemic recovery time for TVD vs FP (< 3 min)	P < 0.01
TIT (< 3 min): (TP vs FP)	P < 0.01
TIT (< 3 min): SVD (TP) vs FP	P < 0.01
TIT (< 3 min): DVD (TP) vs FP	P < 0.01
TIT (< 3 min): TVD(TP) vs FP	P < 0.01
TIT (< 3 min): SVD vs MVD	P < 0.01

**DISCUSSION**

The limitations of exercise stress testing are well known. However, clinicians do feel that they can detect a false positive test by a shorter time taken for the ST segment to recover to baseline during the recovery phase of the stress test. In our study evaluation of the time course patterns did not aid in differentiating true from false positive tests. Our findings are at variance with the report by Barlow *et al*<sup>5</sup> who pointed out that on ST configuration alone, it was impossible to distinguish non-ischemic ST-T from those of ischemic, and that only by the study of the time course patterns after the cessation of the exercise, was one able to truly make a decision on the positivity or negativity of the test. Our study has shown that this assumption is not true and may be dangerous. Clinicians must resort to further testing before concluding that a test result is a false positive finding; otherwise significant coronary artery disease may be missed. In fact, our study of the time course patterns did give an indication of the severity of the coronary disease as assessed by the percentage stenosis as well as the number of vessels involved: 77% of patients with single, double or triple vessel disease

had high grade stenosis with a prolonged recovery time (greater than 3 minutes). These findings are in keeping with the study conducted by Goldschlager *et al*<sup>6</sup> who showed that prolonged recovery time of the ST segment to baseline levels was indicative of diseased arteries in 85% of patients. In our study all except 2 patients with double vessel disease took longer than 3 minutes to recovery, and 24 of the 27 patients with triple vessel disease took longer than 3 minutes to recover, with 15 patients taking longer than 5 minutes to return to baseline.

Ellestad and co-workers<sup>7</sup> also studied the time-course of ST-segment depression during and after exercise testing in 462 subjects who had coronary angiograms. It was discovered that the patients with the early onset and late offset ST segment depression had a high prevalence of CAD which was significant. This pattern occurred in 41 patients in our study, with 33 having DVD and TVD. We have shown that early onset of ischemic ST depression, profound ST segment displacement, and persistence of the changes late into the recovery phase of exercise were associated with more severe myocardial ischemia and increased the probability of more extensive disease. This was demonstrated in 42 patients in our study, 33 of whom who had DVD and TVD.

Conversely, while time course patterns were useful in confirming severe disease when ST changes were persistent, it clearly did not exclude significant disease when changes were transient or absent, or when only the recovery time (IRT) was used to differentiate TP from FP tests. We have shown that the duration of ST depression (total ischemic time) was more helpful than then ischemic recovery time in delineating true positive from false positive tests. The pattern of ST depression also predicted false positivity since up-sloping changes were more commonly associated with false positivity, while the presence of ST depression across multiple leads suggested more extensive CAD.

Appreciation of the limitations of stress tests and understanding the test result is important in interpreting the EST. Identification of the presence and severity of CAD with the EST is limited by poor sensitivity of electrocardiographic tests often leading to requests for Myocardial perfusion imaging (MPI) studies to estimate the extent and severity of CAD. A recent meta-analysis compared the performance of exercise stress test (EST), single photon-emission computed tomographic myocardial perfusion imaging (SPECT-MPI), with both exercise and pharmacologic stress, as well as stress echocardiography in patients with a 25% to 75% pretest risk for coronary disease. Coronary angiography was performed for each positive test<sup>8</sup>. The study reported that EST had a sensitivity of 68% and specificity of 77%, thallium SPECT-MPI a sensitivity of 88% and specificity of 77% and

stress echocardiography a sensitivity of 76% and specificity of 88% in the diagnosis of CAD. Clearly all these tests lack adequate specificity. Although SPECT imaging is better it is not ideal and one reason for this is that coronary angiography reveals epicardial disease and does not detect microvascular disease. When the epicardial vessels are normal, SPECT imaging and the EST may indeed be positive in patients with anginal type pain, due to the presence of small vessel disease in the myocardium<sup>9</sup>. In reality such test results are not false, but true positive due to the presence of microvascular disease that is not detected at angiography. Therefore the clinical profile of the patient and the pretest probability are important in assessing the test result. For example, a subject who is diabetic with a positive stress test and normal coronary angiogram should not be regarded as false positive test. In such instance, SPECT imaging will reveal evidence of ischemia due to microvascular disease.

Several limitations in our study must be mentioned: Use of the exercise ECG for the initial diagnosis of CAD is optimised by exclusion of individuals with left ventricular hypertrophy (LVH), which is known to be associated with false positivity on the EST. In our group nine of the twelve patients with a false positive test had hypertension. Since hypertension is one the commonest major predisposing factors for CHD, these patients could not be excluded from analysis. Even here, we found that the time-course of ST segment changes were not helpful.

Also, only twelve out of 27 patients with non-occlusive atheroma had a Duke Score of greater than 5 (which indicated low risk for cardiac events); so the Duke Score could not provide us with an immediate correlation between risk and non-occlusive atheroma. However, of the remaining 73 patients (with CAD), 63 patients had an intermediate to high risk for future cardiac events. This is important because the predictive value of the exercise stress test depends on the pretest probability of disease and the population at risk<sup>2</sup>.

A further point of interest in this selected sample of subjects (mainly Asian Indians) referred with suspected angina, with their high risk factor profile, was the high pretest likelihood of CAD. In our study the EST had a sensitivity of 89% and a low specificity of 56%. The reason for this high sensitivity is likely due to the fact the unit is a tertiary referral centre receiving a more selected sample with stable angina as well those with atypical symptoms of chest pain for further evaluation. Most of the patients with CAD had true positive ESTs (89%)! The epidemiology of CAD in the migrant Indian has been reported in many studies. As early as 1991 Balarajan<sup>10</sup> showed that people of Indian origin are at high risk and have

one of the highest mortality rates for CHD in the world. In Durban Sewdarsen *et al*<sup>11</sup> and Ranjith *et al*<sup>12</sup> showed an increasing incidence of CAD in young Indian people between 20 to 39 years. This is also reflected in our cohort in whom ten patients with advanced CAD were under 40 years of age.

The low rate of angina during the EST could be attributed to the fact that the patients were on pretreatment with (beta-blockers and/or nitrates), or that they manifested with ST-segment depression without chest pain (silent ischemia). It is well known that patients with diabetes mellitus are prone to painless ischemia, especially if they have peripheral neuropathy<sup>9</sup>. Forty-six patients were diabetic and thirty-four of these had CAD; twenty-nine of these patients with disease did not experience any chest pain during the test.

In this study high post-test diagnostic probability for the absence of coronary artery disease with a negative EST occurred when individual pretest probability of disease (PPD) levels equaled or fell to below 60%, and high post-test diagnostic certainty for CAD was reached for a positive EST when individualized PPD levels equaled or exceeded 89.6%. Therefore the finding of a negative EST in a patient with a high clinical suspicion of angina should be confirmed by other non-invasive tests of ischemia such as SPECT imaging with a stress sestamibi scan.

A recent study has shown that the exercise stress test offers little incremental prognostic value over clinical assessment and the resting ECG in the evaluation of patients with stable chest pain<sup>13</sup>, making it important for the clinician to know exactly why the test is being requested. This does not detract from the value of the exercise stress test in patients with stable chest pain<sup>14</sup> in confirming symptoms, detecting severe disease and in determining safe levels of exercise in subjects with CAD, provided the user understands the limitations of the exercise electrocardiogram and the high rate of false positive and false negative tests<sup>15,16</sup>.

## CONCLUSION

Exercise stress testing is limited by frequent false-negative responses in patients with clinically suspected coronary disease, as well as false-positive results in asymptomatic subjects<sup>17</sup>. Exaggerated responses in the blood pressure during the stress test have been shown not to be consistently associated with false positive tests<sup>18,19</sup>. Our study has shown that time course patterns could not reliably distinguish a true positive test from a false-positive one; instead our study confirms that up-sloping changes during the recovery phase often point to a false positive test. Better assessment of the test result could be obtained from the total ischemic time than the time to recovery of the ST changes. The EST is more

likely to be abnormal in patients with more severe coronary arterial obstruction, more extensive disease, and after more strenuous levels of exercise. These findings need to be confirmed in a larger cohort across a wide spectrum of pretest probability, prospectively under standardized conditions at source of referral.

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