

# Clinical Usefulness of Exercise-Induced ST-Segment Depression Occurring or Increasing during the Recovery Phase

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## SUMMARY

### Background

Despite the current availability of diagnostic image tests with excellent diagnostic and prognostic accuracy, exercise stress testing (EST) remains as the procedure most commonly used for the evaluation, diagnosis and risk stratification of patients with coronary artery disease (CAD).

### Objective

1) To investigate the clinical usefulness of significant exercise-induced ST-segment depression (ST-d) occurring or increasing during the recovery phase of exercise stress test and to compare it with significant ST-segment depression presenting during the active phase of exercise; 2) to evaluate the clinical data and the information provided by EST and coronary angiography.

### Material and Methods

Clinical and EST data from 147 patients with positive stress test were analyzed. All patients had significant ST-segment depression and were divided into three groups: GI, 94 patients with ST-d during exercise; GII, 29 patients with ST-d only during the recovery phase; and GIII, 24 patients with borderline ST-d during exercise which became significant during the recovery phase. The results of the EST were correlated with the coronary angiography findings in each group.

### Results

A diagnosis of significant CAD was made in 78 patients in GI (82.9%), in 22 in GII (75.8%) and in 21 in GIII (87.5%) ( $p = 0.52$ ). Patients in GIII were older, with high prevalence of dyslipidemia, history of previous infarction and three-vessel and/or left main coronary artery disease. GII presented the higher number of asymptomatic patients with one-vessel disease and high prevalence of CAD.

### Conclusions

There were no statistical differences in the percentage of patients with significant CAD among the groups. Patients in GIII had high prevalence of significant and severe CAD. A proper evaluation of ST-d occurring or becoming significant during the recovery phase provided additional clinical information to the results of the EST.

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**Key words >** Exercise Stress Test - ST-Segment Depression - Recovery Phase

## Abbreviations >

<b>AVA</b>	AHereditary family history	<b>GIII</b>	Group III
<b>PTCA</b>	Transluminal coronary angioplasty	<b>HBP</b>	High blood pressure (Hypertension)
<b>MRS</b>	Myocardial revascularization surgery	<b>AMI</b>	Acute myocardial infarction
<b>DLP</b>	Dyslipidemia	<b>BMI</b>	Body mass index
<b>DM</b>	Diabetes mellitus	<b>ST-d</b>	ST-segment depression
<b>CAD</b>	Coronary artery disease	<b>OBS</b>	Obesity
<b>ECG</b>	Electrocardiogram	<b>EST</b>	Exercise stress testing
<b>LVEF</b>	Left ventricular ejection fraction	<b>SMK</b>	Smoking
<b>GI</b>	Group I	<b>LMCA</b>	Left main coronary artery
<b>GII</b>	Group II		

## BACKGROUND

Ischemic heart disease is considered one of the most common causes of disability and mortality in Western countries. For that reason, great efforts are being made to improve identification of patients at high risk for an acute coronary event. (1)

At present, the studies available that include images provide very good diagnosis and assessment of patients with coronary artery disease (CAD), but the exercise stress testing (EST) still remains the most common procedure, because of its easy implementation, reliability, safety, and relatively low cost.

Prior studies showed that the presence of exercise-induced ST segment depression (ST-d) during EST is a good indicator of myocardial ischemia and predictor of acute coronary events, such as unstable angina, acute myocardial infarction, and cardiac sudden death. (2-4)

Although works have been published in which the diagnostic and prognostic value of ST-d occurring only during the recovery phase of exercise stress test (5-11) has been studied, we find no references of studies that have researched on the clinical importance of borderline ST-d during effort, which increases and reaches significant levels in the recovery EST phase, without blood pressure elevation or angina intensity.

The purposes of this study were:

1) to investigate the clinical usefulness of significant exercise-induced ST-d, occurring only during the recovery phase and the ST-d, which is borderline during the active phase of exercise, but then, during post-effort, it increases and becomes positive; then both of them are compared with significant ST-d that occurs during the active phase of exercise.

2) to evaluate the clinical, exercise stress testing data, and compare the EST results with the coronary angiography findings in each one of the patients.

## MATERIAL AND METHODS

In an observational, retrospective study of 2,316 patients who underwent EST in our hospital between March 2008 and July 2010, 147 consecutive patients who met the following inclusion criteria were selected: a) Positive EST when presenting significant ST-d, and b) coronary angiography performed within 6 months after EST. ST-d was considered significant or positive when it was  $\geq 2$  mm to 0.08 sec of the J point, and borderline when it was  $< 2$  mm. (12)

Clinical, exercise stress testing, and coronary angiography findings were analyzed on the basis of medical records, exercise stress test analysis, and results of the cardiac catheterization from the 147 patients divided into three groups, according to the EST phase in which they presented significant ST-d:

Group I (GI): 94 patients (63.9%) with ST-d during exercise phase, who recovered to normal status during post-effort phase, except for 13 patients with a ST slow or delayed recovery of 6 minutes.

Group II (GII): 29 patients (19.7%) with ST-d only during the recovery phase. Group III (GIII): 24 patients (16.4%) with borderline ST-d during exercise phase, which became significant during EST recovery phase.

Before performing the study, the following parameters were evaluated in each patient: age, sex, heart rate, blood pressure, baseline electrocardiogram (ECG), body mass index (BMI), risk factors such as high blood pressure (HBP), diabetes (DM), smoking (SMK), obesity (OBS) when the BMI was  $\geq 30$ , hereditary family history (HFH) of coronary artery disease and dyslipidemia (DLP) if the total cholesterol/HDL cholesterol relationship was  $> 4.5$  and/or triglycerids  $> 150$  mg/dl, three or more risk factors, (13) previous acute myocardial infarction (AMI), history of myocardial revascularization surgery (MRS) or transluminal coronary angioplasty (PTCA), and anti-ischemic medications with beta-blockers, calcium antagonists and/or nitrites.

The main reasons to perform the exercise stress testing were: evaluation of the functional capacity to go to a gymnasium or practise competitive sports, knowing the ischemic threshold in symptomatic patients for angina, atypical precordial chest pain diagnosis under research, periodic control of patients with a history of myocardial ischemic events and/or previous invasive procedures.

Patients with a history of AMI within the 3 months prior to the study, valve disease, hypertrophic cardiomyopathy, atrial fibrillation, ST segment depression on baseline ECG, medications or conditions that affect the conduction and/or ventricular repolarization or baseline ECG interpretation. (14)

The EST was performed with an ergometric bicycle connected to a computer with a continuous register of the 12-lead electrocardiogram. A continuous and progressive protocol was used, which has two phases: the active exercise phase, with stages of 3 minutes each and progressive loads of 150 kgm (330 lbs), and the recovery phase, with 3 stages of 1 minute each during the first 3 minutes, followed by 2 more stages of 3 minutes. (15)

During EST, blood pressure, heart rate, METs achieved, rate pressure product (RPP) and the presence of symptoms reported by the patient were evaluated at the end of each stage. Low effort tolerance was considered when patient reached an ergometric load  $\leq 300$  kgm (330 lbs) /min. and/or had a maximum TTI  $\leq 17,000$  (BPM) (mm Hg). (3, 16)

While in the overall population the EST was considered enough when, during the exercise phase, heart rate reached 85% of the maximum heart rate according to the Robinson table, in patients under beta-blockers therapy it was considered enough when heart rate was over 62% of the maximum heart rate. (17)

Delayed heart rate recovery was considered when, in the second minute of post-effort, heart rate had descended less than 22 beats/minute. (18)

Obstructive lesions in coronary arteries  $\geq 70\%$  and in left main coronary artery (LMCA)  $\geq 50\%$  were considered significant in the coronary angiography. Myocardial contractility impairment was diagnosed when the left ventricular ejection fraction (LVEF) was  $< 40\%$  in the ventriculography performed along with angiography.

EST results were correlated with coronary angiography findings in each group.

## Statistical Analysis

Continuous variables had a normal distribution, are expressed as mean  $\pm$  standard deviation, and were analyzed with the ANOVA test to compare three groups. When differences were found among the groups, Bonferroni post-hoc test was used to determine which groups had the statistically significant difference.

Categorical variables are expressed as frequency and percentage, and they were evaluated with the chi square

test, and partitioning chi squares with degrees of freedom. P value < 0.05 was considered significant.

Sensitivity, specificity, positive and negative predictive values were evaluated, which provided the presence of significant ST-d in each of the groups, with reference of 66 patients with normal EST who underwent coronary angiography within 6 months after EST. Of those 66 patients, 19 (28.8%) had significant CAD of one or more coronary vessels.

A multivariate logistic regression analysis was carried out, including the variables that obtained a  $p < 0.20$  in simple logistic regression to identify the predictive independent variables of significant CAD.

## RESULTS

Table 1 describes the clinical characteristics of patients from each group. Mean age of GIII patients was substantially older (GIII:  $63.5 \pm 8$  years; GI:  $57.5 \pm 8$  years, and GII:  $55.9 \pm 9$  years;  $p = 0.003$ ) and no differences were observed in the distribution by sex.

In all the groups, risk factors with major prevalence were DLP, HBP, and SMK, although only DLP was significantly higher in patients from GIII (79.1% vs 55.3% in GI, and 44.8% in GII;  $p = 0.03$ ).

GIII patients showed more prevalence of previous history of AMI (GIII: 54.1% vs GI: 36.1%, and GII: 20.6%;  $p = 0.01$ ) and of use of anti-ischemic medications (GIII: 91.6% vs GI: 65.9%, and GII: 62%;  $p = 0.03$ ), especially beta-blockers (GIII: 75% vs GI: 51%, and GII: 34.4%;  $p = 0.01$ ).

On the other hand, GII patients showed HFH of coronary artery disease (GIII: 41.2% vs GI: 19.1% and GII: 16.6%;  $p = 0.03$ ). No significant differences were observed in the rest of the variables analyzed. However, GII showed the highest number of patients with three or more risk factors.

Considering the reason for EST, atypical precordial chest pain diagnosis was predominant in patients from GI and GII, whereas GIII patients had a periodic control of their coronary disease, but with no substantial differences among the groups.

Table 2 summarizes the main EST and coronary angiography variables of the patients from each group.

During EST, there were no statistically significant differences in the number of patients who reached maximum load  $\leq 300$  kgm (330 lbs)/min, maximum TTI  $\leq 17,000$ , in the presence of angina, in addition to ST-d and in the delayed recovery of heart rate in post-effort phase. However, it should be pointed out that GIII showed the highest number of patients with low tolerance to exercise and delayed heart rate recovery.

Coronary angiography did not show statistical differences in the number of patients from each group with significant EST. When assessing the number of vessels with severe obstructive lesions, it was found that patients in GII showed a tendency to have more lesion in one vessel, while patients in GIII showed a high prevalence of three-vessel lesion and/or the LMCA (GIII: 58.3%, GI: 34.2%, and GII: 27.5%;  $p = 0.04$ ). Also, GIII was the group that presented the highest percentage of patients with LVEF < 40%, but

did not show substantial differences with GI and GII.

Table 3 details the sensitivity, specificity, and positive and negative predictive values that ST-d diagnosis provided to EST in each of the groups.

Multivariate analysis showed that the only independent variables, predictors of significant CAD, were age, history of previous myocardial infarction, and beta-blockers medications (Table 4).

## DISCUSSION

Previous studies have demonstrated the reliability and clinical importance of the data provided by EST for diagnosis, prognosis, risk stratification, and treatment of patients with suspected or documented CAD. (2-4)

The diagnostic accuracy of CAD and the prognostic value of cardiac sudden death, particularly in hypertensive patients, smokers, and patients with dyslipidemia of significant ST-d that is only present in the recovery phase of EST, have been proved in previous works. (5-10) It has also been pointed out that the ST-d is a sign of acute subendocardial ischemia and of extensive and severe CAD, which is significant when the EST effort phase is over, but it increases even more during the first minutes of the recovery phase. (19)

The results of our study confirm the clinical value of the presence of ST-d, which occurs only in the EST recovery phase; these results show the importance of the ST-d diagnosis, which is borderline during the exercise phase but increases and is significant in the post-effort phase, with no changes in the increase of angina or blood pressure, as opposed to the hypertensive-hyper painful described above, in which the stressed ST-d that some patients developed during the EST recovery phase coincided with increased blood pressure and angina. (20)

Although what causes the ischemic ST-d which occurs only during the EST recovery phase have not been defined yet, Dimsdale et al (21) consider that during the post-effort phase some patients maintain high levels of plasmatic catecholamines, which increase the myocardial demand of oxygen because they increase the myocardial contractility and the risk of acute ischemia, since it produces an imbalance between supply and demand in the coronary arteries with significant obstruction.

No significant differences were observed in the number of patients from the groups who had angina and ST-d during EST. Previous studies have demonstrated that the presence of angina together with ST-D during an EST is a strong predictor of acute coronary events, and that silent ischemia has a similar prognostic value, particularly in hypertensive patients, smokers, and patients with dyslipidemia. (22, 23)

The correlation between the EST result and the analysis of the coronary angiography showed no statistical differences in the percentage of patients

Clinical characteristics	GI (n = 94)	GII (n = 29)	GIII (n = 24)	p
Age (years)	57.5 ± 8.4	55.9 ± 9.1	63.5 ± 8.7	0.003
Sex (men)	71 (75.6%)	21 (72.4%)	19 (79.1%)	0.85
Reason for exercise stress test				
Evaluation of functional capacity	6 (6.4%)	5 (17.2%)	1 (4.1%)	0.13
Atypical precordial chest pain under study	36 (38.3%)	11 (37.9%)	6 (25%)	0.46
Angina pectoris	21 (22.4%)	6 (20.6%)	8 (33.4%)	0.48
Control of CAD	31 (32.9%)	7 (24.3%)	9 (37.5%)	0.55
History of heart disease				
Previous AMI	34 (36.1%)	6 (20.6%)	13 (54.1%)	0.01
MRS	8 (8.6%)	2 (6.9%)	2 (8.3%)	0.96
PTCA	18 (19.1%)	5 (17.2%)	8 (33.4%)	0.26
Risk factors (RF)				
High blood pressure	68 (72.3%)	17 (58.6%)	15 (62.5%)	0.31
Dyslipidemia	52 (55.3%)	13 (44.8%)	19 (79.1%)	0.03
Smoking	55 (58.4%)	19 (65.5%)	14 (58.3%)	0.78
Obesity	30 (31.9%)	7 (24.3%)	8 (33.4%)	0.69
HFH	18 (19.1%)	12 (41.2%)	4 (16.6%)	0.03
Diabetes	24 (25.5%)	9 (31%)	9 (37.5%)	0.48
≥ 3 HR	49 (52.1%)	16 (55.2%)	11 (45.8%)	0.44
Anti-ischemic medication	62 (65.9%)	18 (62%)	22 (91.6%)	0.03
Beta-blockers	48 (51%)	10 (34.4%)	18 (75%)	0.01
Calcium antagonists	15 (15.9%)	6 (20.6%)	5 (20.8%)	0.48
Nitrites	14 (14.8%)	2 (6.9%)	7 (29.2%)	0.3

**Table 1.** Clinical characteristics and risk factors of patients in each group.

	GI (n = 94)	GII (n = 29)	GIII (n = 24)	p
Maximum load ≤ 300 kgm (330 lbs)/min	22 (23.4%)	6 (20.6%)	8 (33.4%)	0.52
Maximum TTI ≥ 17,000 (BMP).(mm Hg)	17 (18%)	3 (10.3%)	6 (25%)	0.37
EST (+) per angina and ST-d	36 (38.3%)	12 (41.3%)	8 (33.4%)	0.83
CAD	78 (82.9%)	22 (75.8%)	21 (87.5%)	0.52
No lesion	16 (17.1%)	7 (24.2%)	3 (12.5%)	0.52
Lesion in 1 vessel	17 (18%)	10 (34.5%)	3 (12.5%)	0.09
Lesion in 2 vessels	29 (30.7%)	4 (13.8%)	4 (16.7%)	0.1
Three-vessel lesion and/or left main coronary artery	32 (34.2%)	8 (27.5%)	14 (58.3%)	0.04
Delayed recovery of heart rate	18 (19.1%)	5 (17.2%)	8 (33.4%)	0.26
LVEF < 40%	22 (23.4%)	5 (17.2%)	9 (37.5%)	0.23

**Table 2.** Main exercise stress testing and coronary angiography data in each group.

with significant CAD in each group.

However, when considering the number of coronary vessels with significant obstructive lesion in patients from each group, we observed that GIII patients had the highest prevalence of three-vessel lesion and/or LMCA, evidencing the presence of extensive and severe CAD. Also, GIII was the group that showed the highest number of patients with LVEF < 40%, but did not show a statistically significant difference with GI and GII.

The lesion in a coronary vessel was predominant in GII patients, which matches the results published by Rashid et al. (11) When comparing our results with those reported in previous works, we observe that the percentage of GI and GII patients with significant CAD was slightly lower than the percentage referred by Lanza et al (10), and by Rashid et al (11) (GI: 82.9% vs Lanza 85%, and Rashid 93%; GII: 75.8% vs Lanza

78%, and Rashid 85%.

This difference may be attributed to the fact that the ST-d ≥ 1 mm to 0.08 sec of J point and coronary obstructions > 50% were considered significant in most of the works. Conversely, our protocol was more selective when considering as significant the ST-d ≥ 2 mm to 0.08 sec of point J and obstructive lesions in coronary arteries ≥ 70%. (2-11)

GII had the highest number of asymptomatic patients who were performed EST to evaluate the functional capacity to go to a gymnasium or practise competitive sports, but it was also the group with the highest number of patients with ≥ three risk factors and high prevalence of HFH of coronary artery disease as risk factor.

Instead, GIII was made up by older patients, with higher prevalence of dyslipidemia, previous history of AMI, and despite being under anti-ischemic therapy,

**Table 3.** Sensitivity, specificity and predictive value of exercise stress testing in each group.

	GI	GII	GIII
Sensitivity	80.4%	52.5%	53.7%
Specificity	74.8%	94%	87%
Positive predictive value	83%	88%	76%
Negative predictive value	71%	71%	71%

**Table 4.** Results of multivariate analysis

Variable	OR	CI 95%	p
Age	1.02	1.00-1.07	0.049
Previous myocardial infarction	4.44	1.96-10.1	0.0004
Medication with beta-blockers	4.74	1.47-15.3	0.009
Group (II/I)	0.9772	0.34-2.79	0.96
Group (III/I)	1.5145	0.52-4.37	0.44

91.6% of them showed the lowest tolerance to exercise during EST.

Significant ST-d diagnosis that occurs or becomes positive during EST recovery phase provided more specificity and similar positive and negative predictive values to EST than the presence of significant ST-d during the active phase of exercise.

Among the study limitations, let us mention the reduced number of patients in GI and GII, and the lack of follow-up in patients to prove the prognostic value of ST-d in the patients from each group.

## CONCLUSIONS

The results of this study show that the presence of significant ST-d in an EST occurring only in the recovery phase, and the borderline ST-d during the exercise phase but then increasing and becoming positive in the post-effort phase has a value and clinical importance similar to the significant ST-d present during the active phase of exercise. For that reason, we consider that its correct assessment increases and improves the clinical information provided by the EST and draws a line under the wrong diagnosis that has considered its presence as a "false positive" response by the EST.

## RESUMEN

**El infradesnivel del segmento ST que se presenta o se profundiza durante la fase de recuperación: su aporte a la utilidad clínica de la ergometría**

### Introducción

No obstante la disponibilidad actual de estudios por imágenes que brindan una muy buena capacidad diagnóstica y de evaluación, la prueba ergométrica graduada (PEG) está reconocida como un estudio importante y continúa siendo el procedimiento más utilizado para la evaluación, el diagnóstico y la estratificación de riesgo de los pacientes con enfermedad arterial coronaria (EAC).

### Objetivo

1) Investigar el valor clínico de la presencia durante una ergometría del infradesnivel del segmento ST (infra-ST) significativo que aparece sólo durante la fase de recuperación o del que es dudoso durante la fase de ejercicio pero que se profundiza tornándose positivo durante la fase de recuperación de la PEG y compararlos con el infra-ST significativo que se presenta durante la fase activa de ejercicio. 2) Evaluar los datos clínicos, ergométricos y de la angiografía coronaria de los pacientes.

### Material y métodos

Se analizaron los datos clínicos y ergométricos de 147 pacientes con PEG positiva por infra-ST significativo, que en 94 pacientes (GI) se presentó durante la fase de ejercicio, en 29 (GII) sólo en la fase de recuperación y en 24 (GIII) fue dudoso durante el ejercicio, pero se profundizó tornándose significativo en la fase de recuperación. En cada grupo se realizó una correlación entre los resultados de la PEG y los hallazgos de la coronariografía.

### Resultados

Se diagnosticó EAC significativa en 78 pacientes del GI (82,9%), 22 del GII (75,8%) y 21 del GIII (87,5%) ( $p = 0,52$ ). El GIII reunió los pacientes de edad más avanzada y con alta prevalencia de dislipidemia, antecedente de infarto previo y lesión de tres vasos y/o del tronco de la coronaria izquierda. El GII presentó el mayor número de pacientes asintomáticos, con lesión de un vaso y alta prevalencia de historia familiar de EAC

### Conclusión

No se observaron diferencias estadísticas en el porcentaje de pacientes con EAC significativa entre los grupos. Los pacientes del GIII mostraron alta prevalencia de enfermedad coronaria extensa y grave. La evaluación correcta del infra-ST que aparece o se profundiza durante la fase de recuperación aumentó la información clínica que aporta una ergometría.

### Palabras clave >

Prueba ergométrica graduada -  
Infradesnivel - Segmento ST -  
Fase de recuperación

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#### Dedication

We dedicate this work to the memory of our dearest Dr. Luis A. Vidal, who left us the legacy of his capacity to observe, his pragmatism, and his balanced judgement in making decisions that provided the best treatment for patients.